1973

Cycloaddition Reactions of Nitrones.

Joyner Sims
Louisiana State University and Agricultural & Mechanical College

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CYCLOADDITION REACTIONS OF NITRONES

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the Degree of

Doctor of Philosophy

in

The Department of Chemistry

by

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A.A., Chipola Junior College, 1963
B.S., Florida State University, 1965
M.S., Florida State University, 1966

August, 1973

For Nina and Myla

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ABSTRACT

Reactions of C-phenyl-N-methylnitrone and other disubstituted nitrones with many monosubstituted alkenes have been reported in the literature. The only products of these reactions are the 5-substituted isoxazolidines regardless of the nature of the alkene. Steric arguments have been proposed to account for these results. We have investigated the reactions of the sterically unencumbered N-t-butylnitrone to demonstrate that electronic effects defined by frontier orbital theory and not steric effects control regioselectivity in nitrone cycloadditions.

N-t-butylnitrone was reacted with the following alkenes: nitroethylene, methyl acrylate, methyl methacrylate, acrylonitrile, methacrylonitrile, 1-acetoxy-1-cyanoethylene, styrene, α-methylstyrene, trans-β-methylstyrene, phenyl vinyl sulfide, isobutyl vinyl ether, vinyl acetate, and 4-phenyl-1-butene. Only the 5-substituted isoxazolidines were formed. This type of product indicates that steric effects do not control regioselectivity. N-t-Butylnitrone was also reacted with the following alkenes and alkynes: phenylacetylene, 5-phenyl-1-pentyne, methyl trans-crotonate, methyl trans-cinnamate, and trans-crotonaldehyde. The disubstituted alkenes gave a mixture of regioisomers for each reaction. Phenylacetylene gave 2-t-butyl-5-phenyl-Δ^4-isoxazoline and 5-phenyl-1-pentyne gave only 1-t-butyl-2-(4-phenylbutyryl)-aziridine.

Frontier orbital theory predicts that very electron deficient alkenes and alkynes should show a loss or reversal of regioselectivity in reactions with nitrones. In accord with these ideas, reactions of N-t-butylnitrone with cyanoacetylene, ethyl propiolate, and phenyl

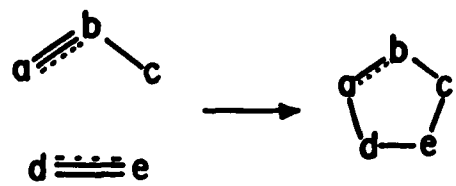
vinyl sulfone gave a mixture of the 4- and 5-substituted isoxazolidines and isoxazolines. Similarly, the reaction of C-phenyl-N-methylnitrone and phenyl vinyl sulfone gave a mixture of regioisomers. Reactions of C-phenyl-N-methylnitrone with cyanoacetylene and nitroethylene were regioselective for the formation of the 4-substituted isoxazoline and isoxazolidine, respectively. These results are uniquely compatible with a frontier orbital theory interpretation of regioselectivity.

N-t-Butylnitrone reacts with 6,6-dimethylfulvene, 6,6-diphenylfulvene, and 6-methyl-6-phenylfulvene to give 1:1 and 2:1 adducts. The 1:1 adducts are only the thermally allowed [4+2] cycloadducts. Reactions of C-phenyl-N-methylnitrone with these fulvenes also gave the thermally allowed 1:1 adducts. The periselectivity of these reactions is shown to be compatible with frontier orbital theory.

I. INTRODUCTION

PART A 1,3-Dipolar Cycloadditions

A 1,3-dipole is defined as a formally zwitterionic molecule, $a^{\equiv}b^{+}-c^{-}$, which undergoes 1,3- addition to an alkene or alkyne, $d^{=}e$, (the dipolarophile) to form a five-membered ring heterocycle.[1] Reactions of 1,3-dipoles with dipolarophiles have been developed into generally useful methods for five-membered heterocycle syntheses because many 1,3-dipoles are readily available and are reactive with most alkenes and alkynes.



In 1938, Smith[2] reviewed the available data on 1,3-additions without distinguishing between cycloadditions and additions of bases, H-B. Only a few papers on 1,3-additions appeared in the literature during the next twenty years. In 1957, Huisgen and coworkers began extensive studies which have led to a clear classification of dipolar reagents and to a recognition of their synthetic utility. The two all-octet resonance forms of the most common 1,3-dipoles are shown in Table I.[3]

The mechanisms of 1,3-dipolar cycloadditions have been thoroughly investigated. Additions of 1,3-dipoles to alkenes are stereospecifically suprafacial and only the thermally allowed $[\pi^4_s + \pi^2_s]$

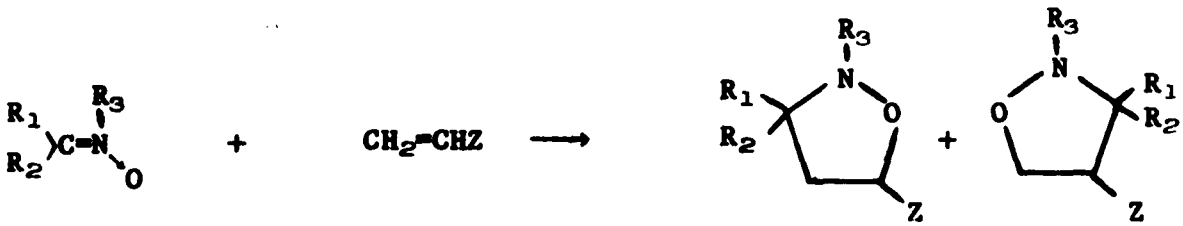
TABLE I

THE COMMON 1,3-DIPOLES

Nitrilium Betaines			
$R-C\equiv\overset{+}{N}-\bar{C}R_2$	$\longleftrightarrow$	$R-\bar{C}=\overset{+}{N}=CR_2$	Nitrile ylides
$R-C\equiv\overset{+}{N}-\bar{N}R$	$\longleftrightarrow$	$R-\bar{C}=\overset{+}{N}=NR$	Nitrile imines
$R-C\equiv\overset{+}{N}-\bar{O}$	$\longleftrightarrow$	$R-\bar{C}=\overset{+}{N}=O$	Nitrile oxides
Diazonium Betaines			
$N\equiv\overset{+}{N}-\bar{C}R_2$	$\longleftrightarrow$	$\bar{N}=\overset{+}{N}=CR_2$	Diazoalkanes
$N\equiv\overset{+}{N}-\bar{N}R$	$\longleftrightarrow$	$\bar{N}=\overset{+}{N}=NR$	Azides
$N\equiv\overset{+}{N}-\bar{O}$	$\longleftrightarrow$	$\bar{N}=\overset{+}{N}=O$	Nitrous oxide
Azomethinium Betaines			
$R_2C=\overset{+}{N}(R)-\bar{C}R_2$	$\longleftrightarrow$	$R_2\bar{C}-\overset{+}{N}(R)=CR_2$	Azomethine ylides
$R_2C=\overset{+}{N}(R)-\bar{N}R$	$\longleftrightarrow$	$R_2\bar{C}-\overset{+}{N}(R)=NR$	Azomethine imines
$R_2C=\overset{+}{N}(R)-\bar{O}$	$\longleftrightarrow$	$R_2\bar{C}-\overset{+}{N}(R)=O$	Nitrones
Oxygenated Dipoles			
$R_2C=\overset{+}{O}-\bar{C}R_2$	$\longleftrightarrow$	$R_2\bar{C}-\overset{+}{O}=CR_2$	Carbonyl ylides
$R_2C=\overset{+}{O}-\bar{N}R$	$\longleftrightarrow$	$R_2C-\overset{+}{O}=NR$	Carbonyl imines
$R_2C=\overset{+}{O}-\bar{O}$	$\longleftrightarrow$	$R_2\bar{C}-\overset{+}{O}=O$	Carbonyl oxides
$O=\overset{+}{O}-\bar{O}$	$\longleftrightarrow$	$\bar{O}-\overset{+}{O}=O$	Ozone

and $[\pi 6_s + \pi 4_s]$ additions to trienes have been observed.[4] Solvent polarity has little effect on reaction rates, and 1,3-dipolar cycloadditions have small activation enthalpies and large negative activation entropies. These facts are considered totally compatible only with a concerted four-center mechanism.[5,6]

The experimentally observed regioselectivity (selectivity in the direction of addition to an unsymmetrical alkene or alkyne) of most 1,3-dipolar cycloadditions has been the most difficult phenomenon to explain. The reaction of nitrones (1) with monosubstituted alkenes (2)



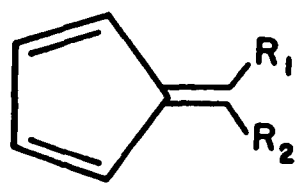
1 2 3

is exemplary of the phenomenon. Prior to our work, nitrone cycloadditions to unsymmetrical alkenes had always been observed to give the 5-substituted isoxazolidines (3) regardless of the nature of the alkene substituent, Z.

Firestone[7] proposed a diradical mechanism to account for these observations; however, Huisgen[5,8] has convincingly argued that the mechanism of nitrone and other 1,3-dipolar cycloadditions is generally concerted. In the absence of a stronger argument, Huisgen[9] has proposed that steric repulsions between a carbon substituent on the nitrone and the alkene substituent, Z, favor formation of the less sterically hindered 5-substituted isoxazolidine (3). Houk et al.,[10] have recently proposed a qualitative theory to rationalize reactivity,

regioselectivity, and periselectivity in 1,3-dipolar cycloadditions. The theory suggests that regioselectivity is produced by electronic rather than steric factors. The first goal of this research was to test this idea for one class of reactions of this type, the cycloadditions of nitrones. To this end, reactivity and regioselectivity studies for reactions of alkenes and alkynes with the sterically unencumbered N-t-butylnitrone (1, R_1=R_2=H, R_3=t-butyl) and with C-phenyl-N-methylnitrone (1, R_1=H, R_2=Ph, R_3=Me) were carried out.

A second goal of this research was to study the phenomenon of periselectivity (selective formation of one of the thermally allowed products) in nitrone cycloadditions. To this end, the cycloadditions of nitrones with fulvenes were investigated. Fulvenes (4) are cyclic trienes which generally exhibit strong "olefinic character". They have



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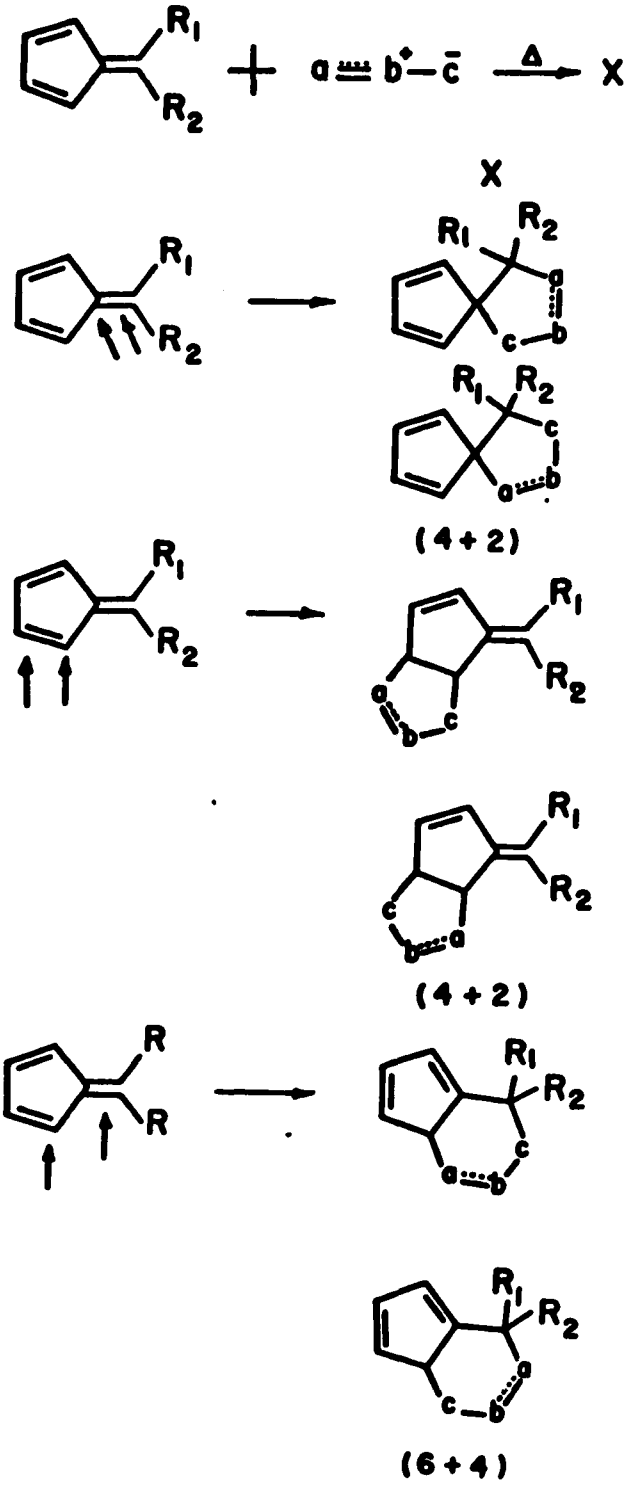
been used as the subject of numerous theoretical and synthetic studies.[11] No reactions of fulvenes and nitrones have been reported in the literature. Orbital symmetry selection rules clearly predict that concerted reactions may occur between fulvenes and 1,3-dipoles. The thermally allowed products for the reaction of a fulvene with a 1,3-dipole, $a^{4s}b^{+}\!\!-\!\!c^{-}$, are shown in Figure 1. Orbital symmetry selection rules do not reveal which of the several possible adducts is most favored. Houk et al.,[10] have recently applied perturbation theory to the

Figure 1. The Thermally Allowed Products for the Reaction of Fulvenes and 1,3-Dipoles.

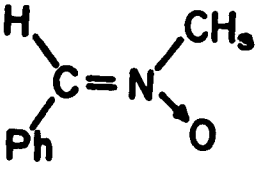


prediction of the most favored adduct in these reactions. To confirm these predictions, reactions of N-t-butylnitrone and C-phenyl-N-methylnitrone with 6,6-dimethyl-, 6,6-diphenyl-, and 6-methyl-6-phenylfulvene were investigated.

PART B Structure and Synthesis of Nitrones

The synthesis of azomethine N-oxides (nitrones) was first reported by Beckmann in 1889. Nitrones were formed in the attempted O-alkylation of oximes.[12] In 1916, Pfeiffer[13] suggested the name "nitrone", a contraction for nitrogen ketone, for these N-alkylated oximes. The name was chosen because of the many similar reactions of nitrones and ketones. The structures of these compounds were well established by 1938.[2] The π electrons of nitrones are contained in a resonance stabilized four electron system, isoelectronic with the allyl anion system. The two all-octet structures (Table I) appear to make the most significant contributions to the resonance hybrid.[1,10] Structural formulas are frequently written in the manner illustrated by Structure 5.

Nitrones may exist as a pair of geometrical isomers because of the CN double bond in the nitrone group. C-Phenyl-N-methylnitrone (5), for example, exists only as the trans-isomer.[14] Emmons[15] has



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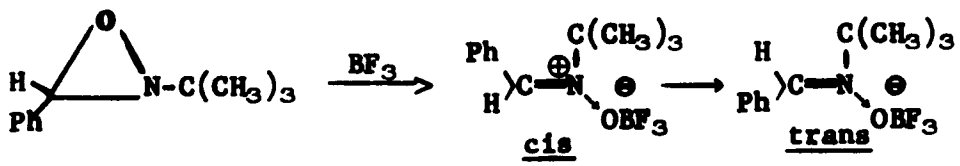
reported the only example of geometric isomerism in aldonitrones [RCH=N(O)R′]. The boron trifluoride salt of cis-C-phenyl-N-t-butyl-nitrone (7) was initially formed when 2-t-butyl-3-phenyloxazirane (6) was treated with boron trifluoride. Isomerization to the trans isomer (8) was completed within 24 hours in a benzene solution.



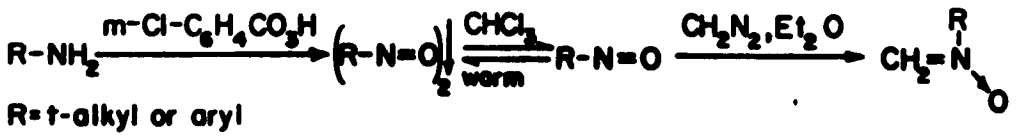
6 7 8

The isomers of some ketonitrones [RR'C=N(O)R"] have been isolated as stable compounds.[16] The configurations of the isomers were established by dipole moment measurements. The cis isomers were readily converted into the trans isomers by heating.

Nitrones can be synthesized by the reaction of N-substituted hydroxylamines with aldehydes or ketones, oxidation of N,N-disubstituted hydroxylamines, condensation reactions of aromatic nitroso compounds with activated methyl or methylene groups, or by alkylation of oximes. The preparations and chemistry of nitrones were reviewed in 1938,[2] 1964,[14] and 1965.[17] The preparations of nitrones were reviewed in 1972.[18] The recent syntheses by Baldwin and coworkers, described below, were not included in the latter reference.

Baldwin[19] reported the first synthesis of stable methylene nitrones in 1968. These nitrones are generally prepared by Scheme A as described by Baldwin. The blue t-nitroso-monomers obtained from the

Scheme A



R=t-alkyl or aryl

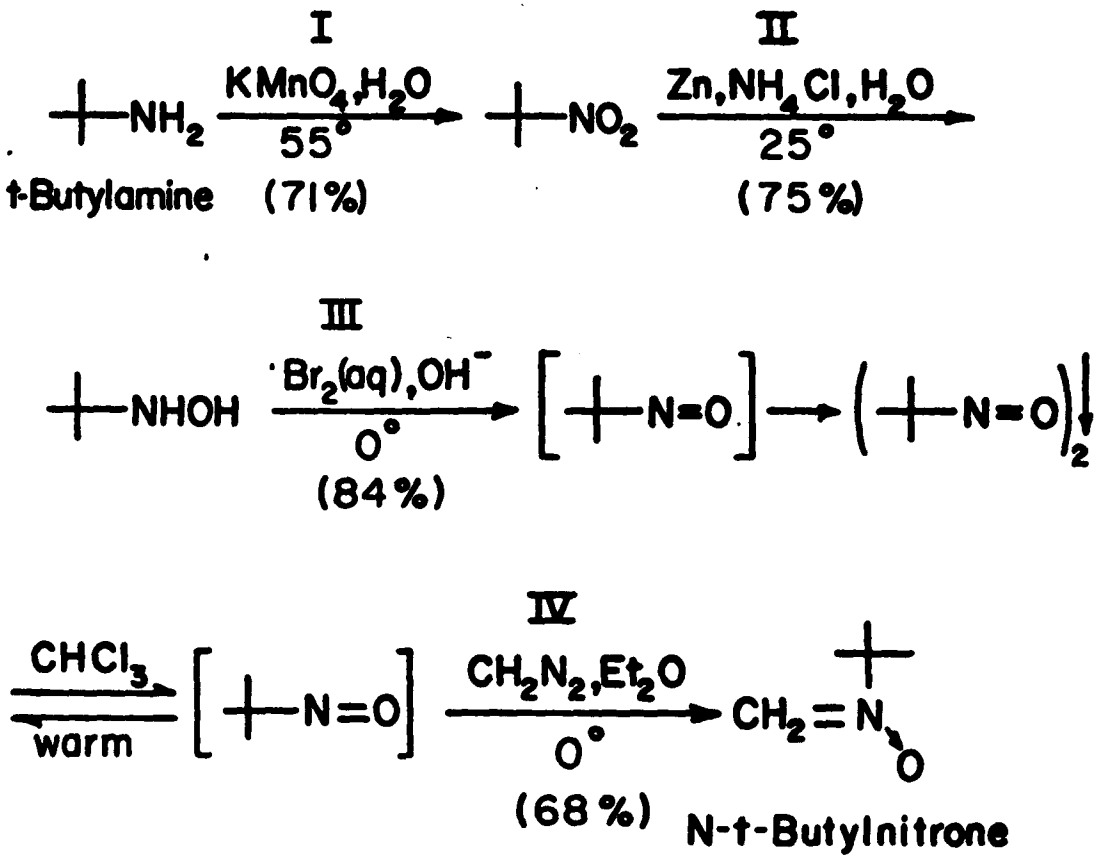
labile dimers are titrated with an ethereal diazomethane solution to afford the methylene nitrones in good yields.* Many dimeric nitroso-compounds are conveniently accessible through oxidation of the parent amines with m-chloroperbenzoic acid in dichloromethane.[20]

No experimental details were available in the literature for the preparation of N-t-butylnitrone used in these studies. Several attempts to prepare and isolate t-nitrosobutane by oxidation of t-butylamine with m-chloroperbenzoic acid were frustrating, apparently because of the great volatility and thermal instability of the t-nitrosobutane monomer.[21] An alternate route to the more stable t-nitrosobutane dimer was developed and is outlined in Scheme B. Reaction yields are enclosed in parentheses. References and experimental details for steps I-IV are given in Section III B.

Baldwin has also recently reported a method for the direct alkylation of nitroso-compounds with oxonium salts.[22] The nitrones are liberated from the intermediate nitrone salts by the addition of base.

*The reactions of diazo-compounds with aromatic nitroso-compounds to produce nitrones were first described in the last century.[14] The reaction of diazomethane and nitroso-benzene to give the dinitrone of glyoxal was reported in 1897.[2]

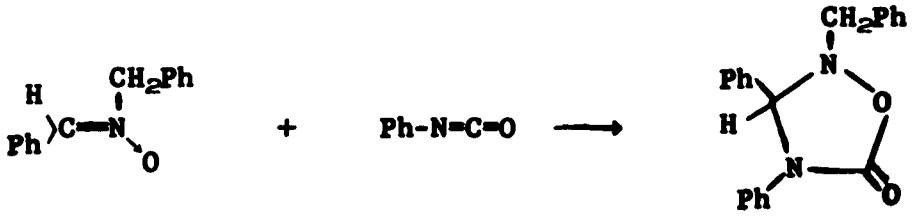
Scheme B


I
II
KMnO4,H2O
55°
Zn,NH4Cl,H2O
25°
t-Butylamine
(71%)
(75%)
III
Br2(aq),OH⁻
0°
(84%)
IV
CHCl3
warm
CH2N2,Et2O
0°
(68%)
N-t-Butylnitrone

PART C Cycloaddition Reactions of Nitrones

1. Synthetic Utility

The reaction of phenyl isocyanate with "N-benzyl-β-benzaldoxime" (9) was studied by Beckmann in 1890 in connection with investigations of oxime isomerism.[23] Apparently, this is the first reported 1,3-dipolar cycloaddition reaction of nitrones. The adduct was correctly assigned the structure 10, 2-benzyl-3,4-diphenyl-1,2,4-oxadiazolidin-5-one. Staudinger and Meischer[24] reported the reactions of several nitrones

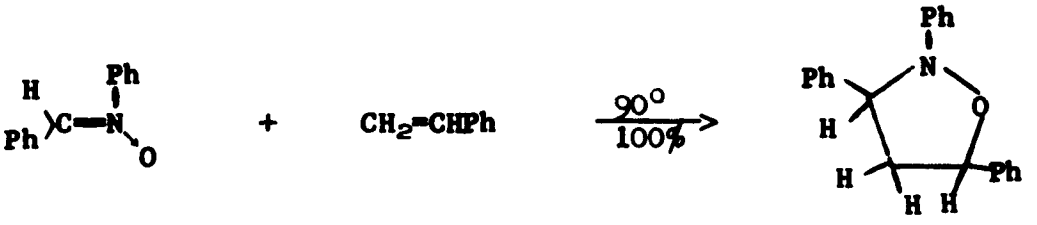


9 10

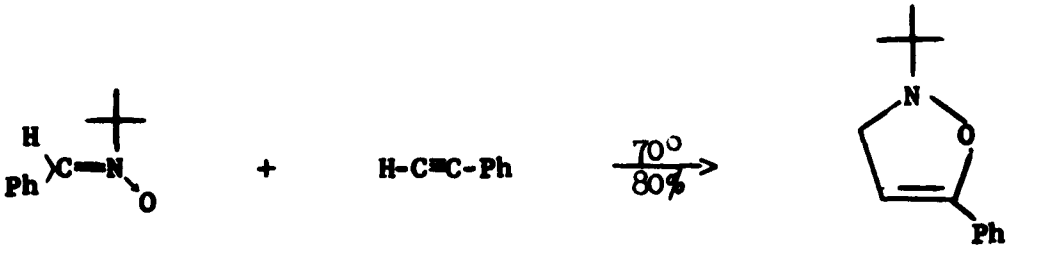
with phenyl isocyanate and diphenylketene in 1919; however, the structures of reported products were incorrectly assigned. In 1938, Smith[2] reviewed the chemistry of nitrones without distinguishing between cycloadditions and additions of bases, H-B. Numerous papers describing preparations of nitrones appeared in the literature during the next twenty years, but no cycloaddition reactions of nitrones were reported.[14,17] In 1957, Huisgen and coworkers began extensive studies which have led to a clear classification of dipolar reagents and to a recognition of their synthetic utility.[1]

The cycloaddition reactions of nitrones with alkenes, alkynes, and other dipolarophiles generally proceed to give good yields and provide

a convenient route for the synthesis of five-membered heterocycles.[1] C,N-Diphenylnitrone (11) and styrene, for example, react quantitatively at 90° to give 2,3,5-triphenylisoxazolidine (12).[25] N-t-Butylnitrone (13) reacts with phenylacetylene at 70° to give 2-t-butyl-5-phenyl-Δ^4-isoxazoline (14) in 80% yield.[26b] It is not even necessary to use isolated nitrones for many of these reactions. If phenylhydroxylamine

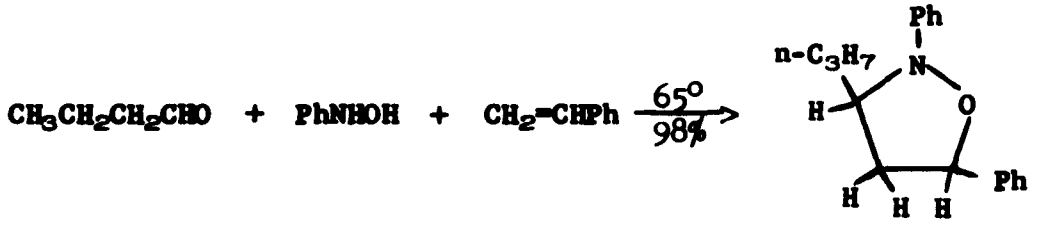


11 12



13 14

and butyraldehyde are combined in the presence of styrene, then C-propyl-N-phenylnitrone adds *in situ* to the alkene to give 15 in 98% yield.[25] If hydroxylamine and formaldehyde are combined in the presence of methyl acrylate, the parent nitrone (a tautomer of formaldoxime) which cannot be isolated in a pure state adds *in situ* to the alkene to give 5-carbomethoxyisoxazolidine (16) in 0.25% yield.[27] *In situ* generation is especially convenient for many nitrones which either cannot be prepared in a pure state or which can be prepared only in low yields.



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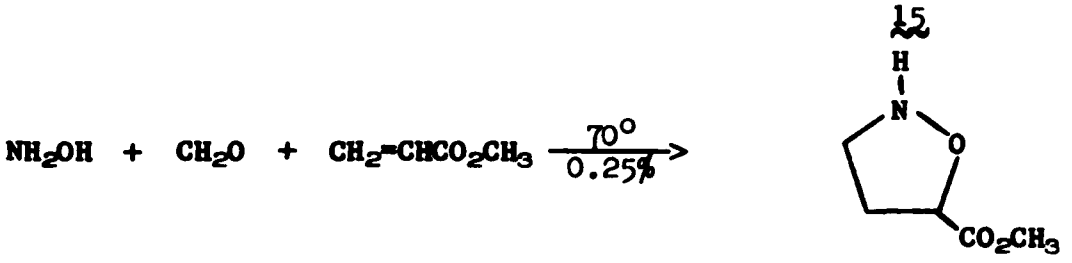
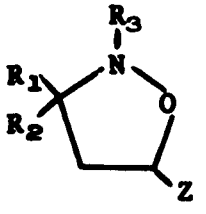


16

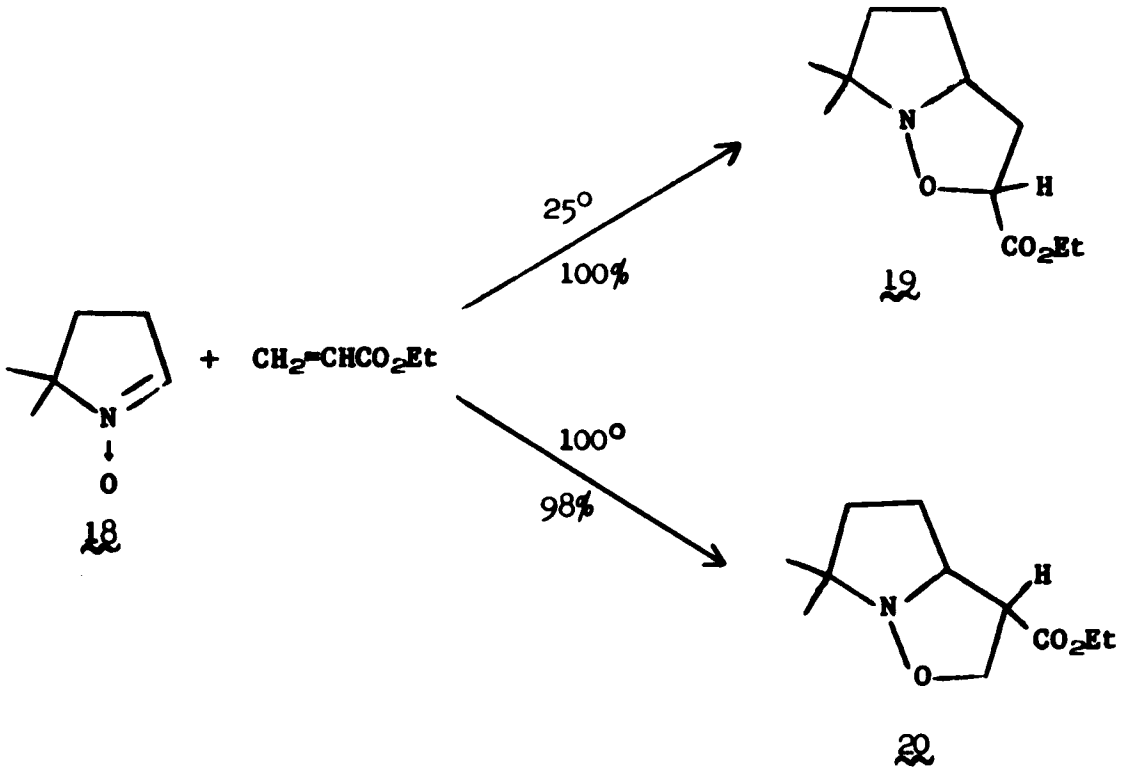
The experimentally observed regioselectivity (selectivity in the direction of addition to an unsymmetrical alkene or alkyne) of nitrone cycloadditions has been the most difficult phenomenon to explain. Prior to our work, nitrone cycloadditions to monosubstituted alkenes had always been observed to give only the 5-substituted isoxazolidines (17) regardless of the nature of the alkene substituent, Z.



17

Many 1,2-disubstituted alkenes as well as alkynes give exclusively the 4-substituted isomers or a mixture of products.[9] These observations will be discussed at length below and in Section II B.

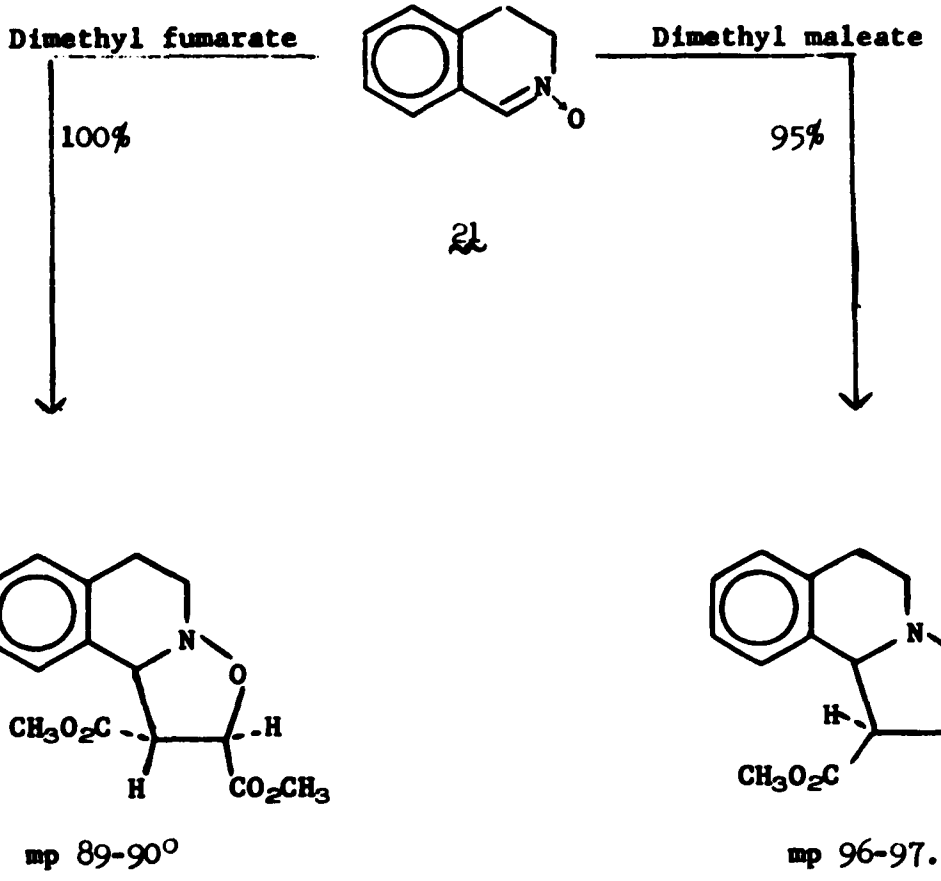
Limited data suggest that nitrone cycloadditions may be subject to kinetic and thermodynamic control. 5,5-Dimethyl-Δ^4-pyrroline N-oxide (18), for example, reacts rapidly with ethyl acrylate at room temperature to give 100% of the 5-substituted isoxazolidine 19 and slowly with the ester at 100° to give 98% of the 4-substituted isoxazolidine (20).[28] No similar data are available in the literature for other nitrone cycloadditions.



2. Mechanism

The mechanisms of 1,3-dipolar cycloadditions have been thoroughly investigated, largely by Huisgen and coworkers.[5] Data for nitrone reactions, given below, are an important part of the total evidence which strongly supports a concerted mechanism for these reactions. The essentially quantitative reactions of 3,4-dihydroisoquinoline N-oxide (21) with dimethyl fumarate and dimethyl maleate are

stereospecifically suprafacial.[29,5] The reaction of C-phenyl-N-methylnitrone (5) and methyl methacrylate in toluene has a small activation

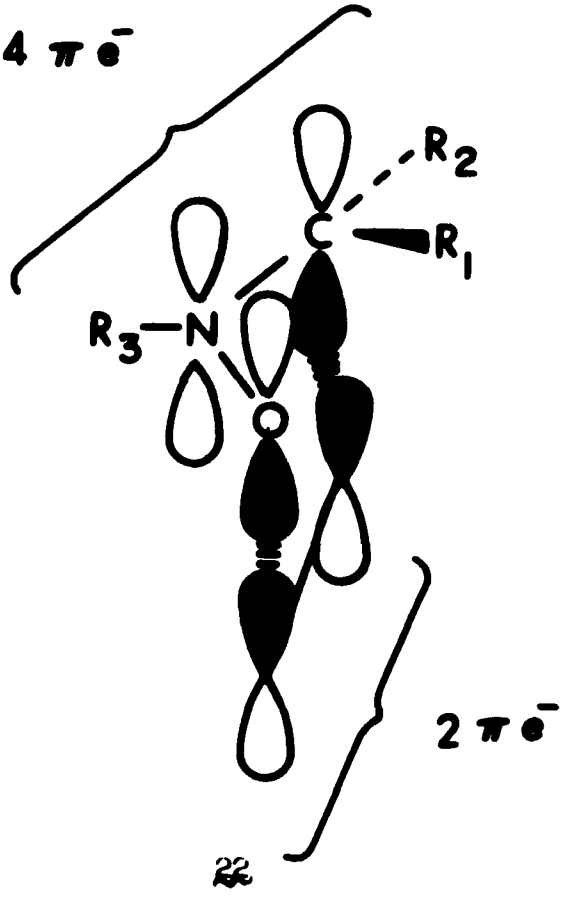


enthalpy (15 kcal/mol) and a large negative activation entropy (-32 eu). Similar Eyring parameters were reported for the reaction of 5 with 2-vinylpyridine.[30,5] Solvent polarity has little effect on the rate of addition of C-phenyl-N-methylnitrone (5) to ethyl acrylate as shown by the data of Huisgen[30] given in Table II. Finally, N-t-butylnitrone reacts with 6,6-dimethyl- and 6,6-diphenylfulvene to give only the thermally allowed $[_{\pi}4_s + _{\pi}2_s]$ cycloadducts.[26b] All of these facts are totally compatible only with a concerted four-center mechanism in which [4+2] π electrons are involved in the cycloaddition process that is shown in formula 22.

TABLE II

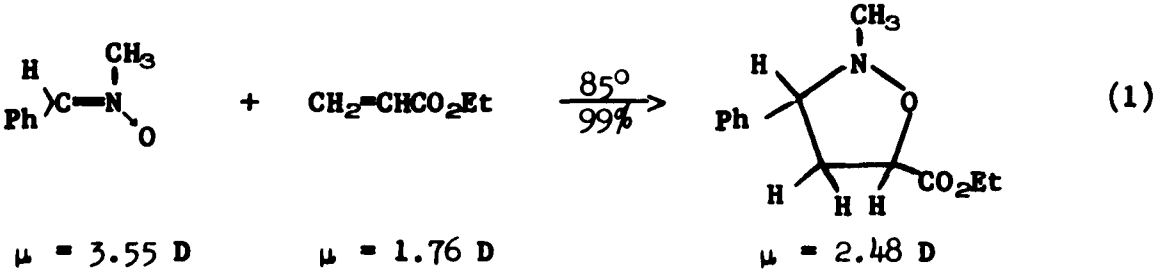
SOLVENT EFFECT DATA FOR THE REACTION OF C-PHENYL-N-METHYLNITRONE AND ETHYL ACRYLATE AT 85°[30]

Solvent	$10^4 k_2$ ($l\text{-}mol^{-1}\text{-}sec^{-1}$)	Dielectric Constant (25°)
Toluene	4.8	2.4
1,2-Dimethoxyethane	2.6	7.0
Pyridine	2.22	12.3
Dimethyl sulfoxide	1.82	48.9
N,N-Dimethylformamide	1.64	36.7
Methoxyethanol	1.12	15.9
Ethanol	0.86	24.3



22

An absence or a small extent of solvent dependence is typical for the rates of concerted cycloadditions. The small rate changes reflected in the data of Table II can be related to an estimated dipole moment for the transition state of the reaction relative to the dipole moments of the reactants and product. Huisgen[5,30] has estimated from calculations that a transition state dipole moment of 5.4 D for the reaction shown in Equation (1) would lead to no dependence of rate on the solvent polarity and that a smaller transition state dipole moment would lead to a small inverse solvent dependence. These data indicate

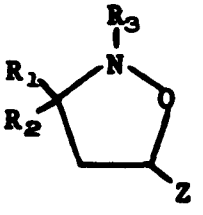


(1)

that nitrone cycloadditions are concerted reactions. Large rate enhancements with increasing solvent polarity should be observed if zwitterionic intermediates were formed in these reactions since such zwitterions would have large dipole moments. The small rate change with increasing polarity of the solvent observed for the reaction of Equation (1) is compatible with a transition state dipole moment of less than 5.4 D. Similar experimental results were obtained in these studies and the data are presented and discussed in Section II B.

The regioselectivity observed in the reactions of nitrones with monosubstituted alkenes has already been mentioned (page 3). In the absence of stronger arguments, Huisgen[9] has proposed that steric

factors favor the formation of the 5-substituted isomers, 23. In the transition state, steric repulsions between the carbon substituents of the nitrone and the alkene substituent Z should be greater for the formation of 24 than for the formation of 23. Firestone[7] proposed a



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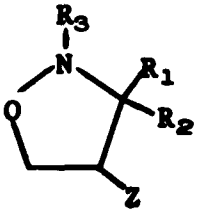

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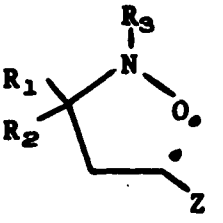

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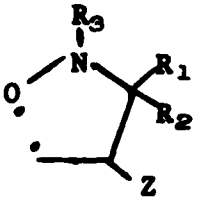
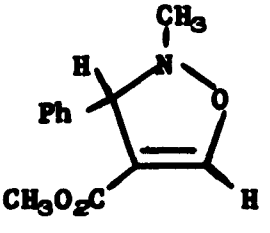


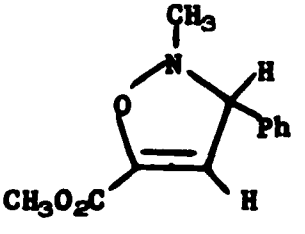
26

diradical mechanism to account for these observations. Presumably the intermediate diradical 25 leading to the formation of 5-substituted adducts (23) is more stable than the intermediate diradical 26 leading to the formation of the 4-substituted isomers (24). However, Huisgen[5,8] has convincingly argued that the mechanisms of nitrone and other 1,3-dipolar cycloadditions is generally concerted.

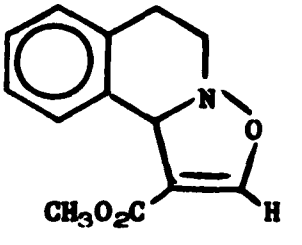
In 1969, Huisgen[31] reported the synthesis of 4-substituted Δ^4-isoxazolines in reactions of nitrones with methyl propiolate. A 58:42 mixture of 27 and 28 was obtained with C-phenyl-N-methylnitrone and only the 4-substituted isomer 29 was obtained with 3,4-dihydroisoquinoline N-oxide. The formation of 27 and 29 is contrary to both the



27



28



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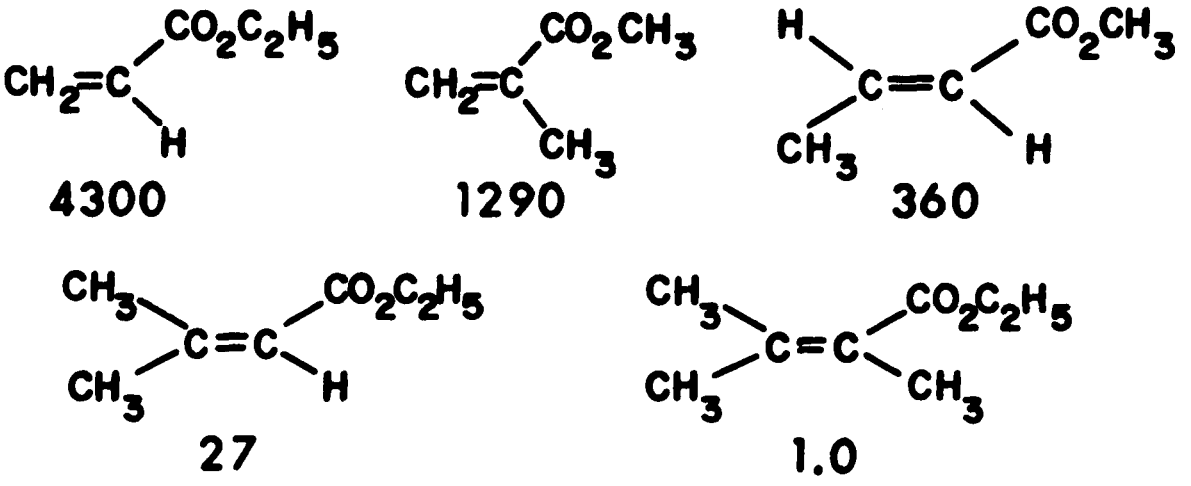
steric arguments of Huisgen and the free radical theory of Firestone. A later discussion in Section II B will show that frontier orbital concepts can adequately account for the formation of these products.

3. Reactivity

The steric and electronic nature of dipoles and dipolarophiles greatly affect the reaction rates of 1,3-dipolar cycloadditions. Huisgen and coworkers have amassed a large volume of data to illustrate this point.[5] Their data for nitrone reactions are given in Figures 2 and 3.

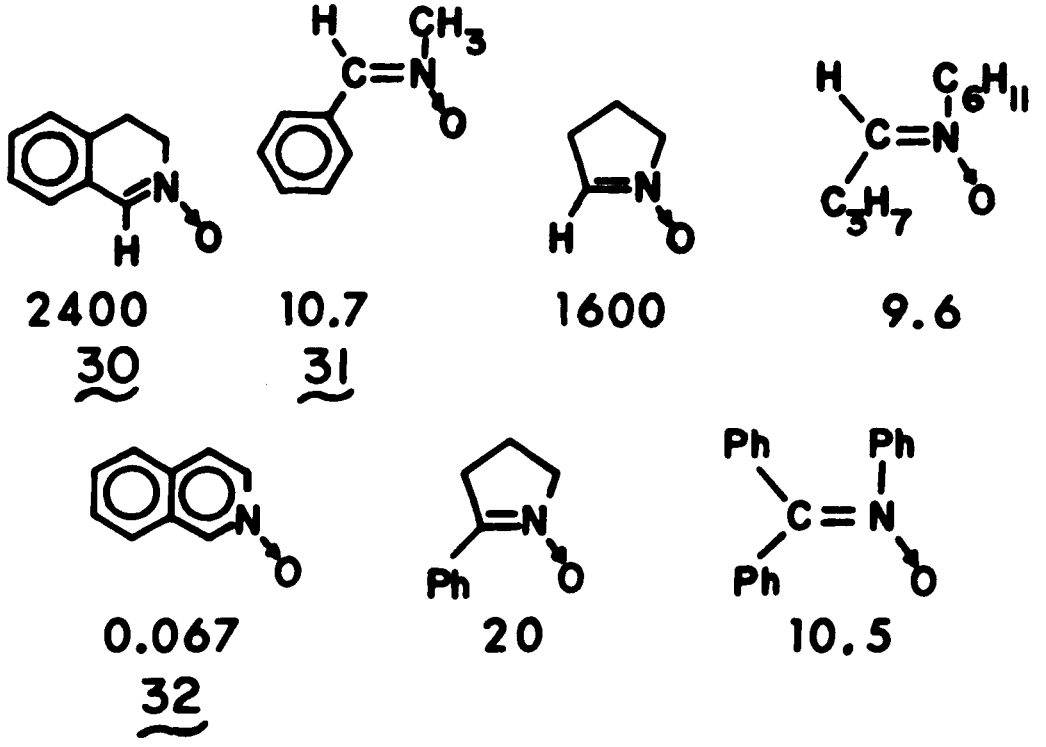
Huisgen has attributed the variation in the reactivity of the methylated acrylic esters shown in Figure 2 largely to steric factors. Methylated acrylic esters should also be electronically less reactive than methyl acrylate according to the recent concepts of frontier orbital theory discussed in Section II A.

The data of Figure 3 illustrate the wide range of reactivity of nitrones with ethyl crotonate. 3,4-Dihydroisoquinoline N-oxide (30) is 224 times more reactive than the electronically similar but sterically different C-phenyl-N-methylnitrone (31). Huisgen[5,30] has attributed this difference to steric factors. 3,4-Dihydroisoquinoline N-oxide (30) is 35,000 times more reactive than the sterically similar but electronically different isoquinoline N-oxide (32). Loss of the aromatic stabilization energy of 32 and of other heteroaromatic N-oxides in cycloaddition reactions causes these nitrones to be much less reactive than their aliphatic counterparts.[5,30] A frontier orbital theory interpretation of the relative reactivities of nitrones is given in Section II B.



$k_2 \times 10^6$ (l-mol^{-1}-sec^{-1}), Toluene, 120°

Figure 2. Rate Constants for Reactions of C-Phenyl-N-Methylnitrone and Methylated Acrylic Esters[5,30]



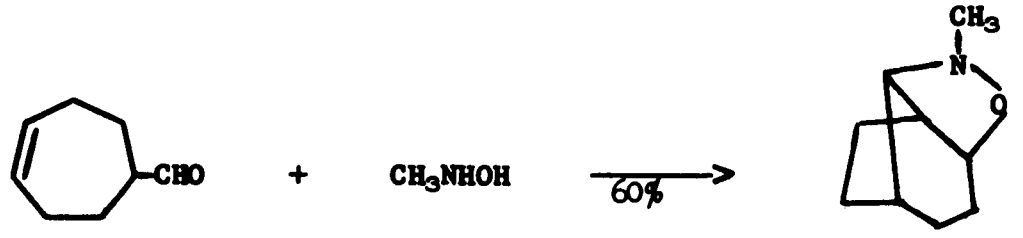
$k_2 \times 10^5$ (l-mol^{-1}-sec^{-1}), Toluene, 100°

Figure 3. Rate Constants for the Reactions of Nitrones and Ethyl Crotonate[5,30]

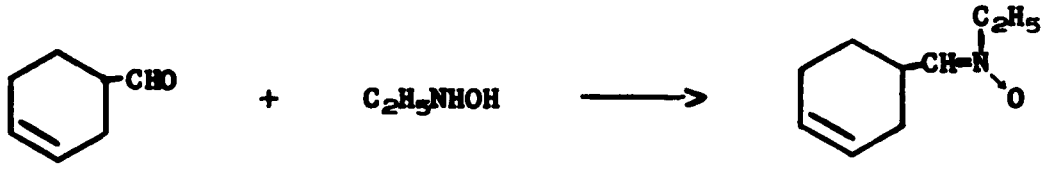
4. Reactions

A literature survey of nitrone cycloaddition reactions is summarized in Tables III-IX at the end of this Section. Several types of reactions not amenable to an abbreviated description are described below.

Intramolecular cycloaddition reactions of nitrones to olefins have been extensively studied by LeBel and coworkers.[32] An example of these reactions is shown below. When 4-cycloheptenecarboxaldehyde (33) was treated with N-methylhydroxylamine, a single product, 34, was obtained in 60% yield. A similar reaction of 3-cyclohexenecarboxaldehyde (35) and N-ethylhydroxylamine gave only the nitrone 36.[32f] Other workers have also reported these kinds of reactions.[33]



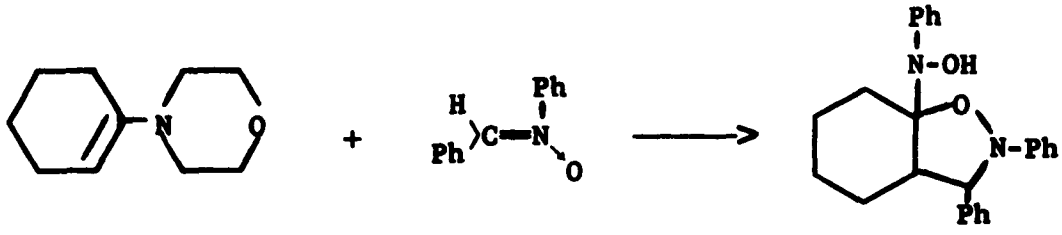
33 34



35 36

The literature contains few references to the reactions of nitrones and enamines. However, the formation of both 4- and 5-substituted isoxazolidines has been observed as summarized and referenced in Table VIII below. Tsuge et al.[34] reported the formation of an

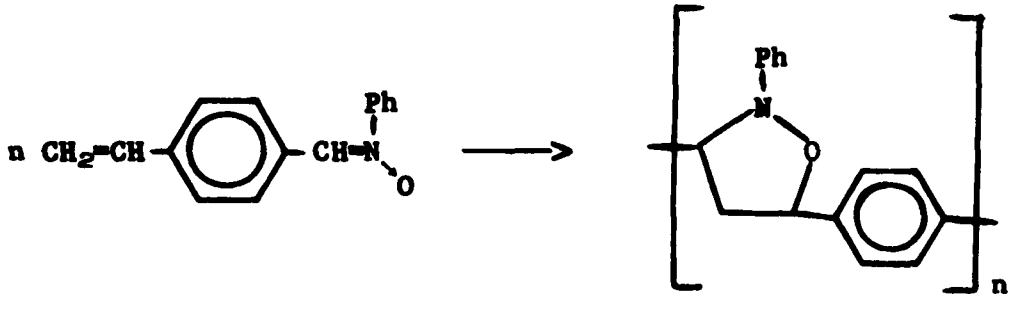
"unusual" product (39) from the reaction of C,N-diphenylnitrone (38) and 1-N-morpholino-1-cyclohexene (37) in refluxing benzene. The same product was obtained in low yield from the reaction of 38 and 1-N-piperidino-1-cyclohexene.[34] Similar results have been observed in



37 38 39

these studies. The reaction of 37 and N-t-butylnitrone gave a white crystalline compound, (mp 108-111°) for which the structure has not been assigned (Sections II B and III C).

Nitrone cycloadditions have been used for the syntheses of polymers. One example is given in Equation 2.[35]



(2)

Nitrones have also been used as radical scavengers in free radical studies.[36]

The photochemical reactions of nitrones including aromatic amine N-oxides have recently been reviewed.[37]

INDEX TO TABLES III-IX

TABLE III

1,3-CYCLOADDITION REACTIONS OF NITRONES WITH UNCONJUGATED ALKENES AND ALKYNES

Alkene or Alkyne	Adduct[1]	Yield, %[2]	Remarks[2]	Ref.[3]
Alkenes				
---------- N-t-Butylnitrone ----------				
4-Phenyl-1-butene	A	87		a
---------- N-Methylnitrone ----------				
1-Pentene	A	64	N	n
trans-2-Pentene	C	42	D,E,N	n
cis-2-Pentene	C	49	D,E,N	n
1-Dodecene	A	24	N	n
---------- N-Ethylnitrone ----------				
Cyclohexene	C	H	N	11
---------- N-1-Ethylcyclohexylnitrone ----------				
Norbornene	C	86		w
Cyclohexene	C	70		w
Bicyclo[4.2.0]oct-7-ene	C	73		w
trans-Cyclooctene	C	92		w
---------- C-Phenyl-N-methylnitrone ----------				
Allyl alcohol	A	99	J	k,l
1-Heptene	A	93	J	k
Allyl acetate	A	76	J	k
Methyl allylacetate	A	98	J	k
Ethyl 9-allylnonanoate	A	67	J	k
Safrole	A	97	J	k

(Continued)

TABLE III (Continued)

C-Phenyl-N-methylnitrone (Continued)				
Cyclopentene	C	89	J	k,l
Cyclohexene	C	78	J	k,l
Norbornene	C	96	J	k,l
Dimethyl 5-norbornene-2,3-dicarboxylate	C	30	J	k,l
2,3-Diazo-5-norbornene	C	88	J	k,l
5-Cyano-5-norbornene	G	50		l
Norbornene	C	74	I	w
Bicyclo[4,2,0]oct-7-ene	C	71	I	w
trans-Cyclooctene	C	H	I	w
Norbornene	C	79	I	aa
3,4-Dihydroisoquinoline N-oxide				
Allyl alcohol	A	75	J	k
Norbornene	C	94	I	w,k,l
Dimethyl 5-norbornene-2,3-dicarboxylate	C	74	J	k
Cyclohexene	C	H		w
Bicyclo[4.2.0]oct-7-ene	C	H		w
C,N-Diphenylnitrone				
1-Hexene	A	93	J	k
Allyl alcohol	A	100	I	k
Norbornene	C	99	I	k
C-Benzoyl-N-phenylnitrone				
Ethylene	C	79		b
Propylene	A	99	J	b
1-Hexene	A	93	J	b

(Continued)

TABLE III (Continued)

C-Benzoyl-N-phenylnitrone (Continued)				
Allyl alcohol	A	84	J	b
Cyclopentene	C	49	J	b
Norbornene	C	35	J	b
C-(p-Nitrobenzoyl)-N-phenylnitrone				
Ethylene	C	90		b
1-Hexene	A	82	J	b
C-(5-Nitro-2-furyl)-N-phenylnitrone				
Allyl alcohol	A	95		ww
Allyl bromide	A	66		ww
Methallyl chloride	A	44		ww
C-(6-Uracilyl)-N-phenylnitrone				
Allyl alcohol	A	100		vv
C-Propyl-N-cyclohexylnitrone				
Norbornene	C	41	J	k
Dimethyl 5-norbornene-2,3-dicarboxylate	C	78	J,N	k
5,5-Dimethyl-Δ^1-pyrroline N-oxide				
Allyl alcohol	A	84		hh
Acryldehyde diethyl acetal	G	Q		hh
Allylacetone	G	H		11
4,5,5-Trimethyl-Δ^1-pyrroline N-oxide				
Cyclohexene	C	H	J	11
2,3,4,5-Tetrahydropyridine N-oxide				
Cyclohexene	C	H	J	11

(Continued)

TABLE III (Continued)

Alkynes

---------- *N*-*t*-Butylnitrone ----------				
5-Phenyl-1-pentyne	P	36	E,K	a
---------- *C*-Phenyl-*N*-methylnitrone ----------				
Benzyne	C	100		e
---------- 3,4-Dinhdroisoquinoline *N*-oxide ----------				
Benzyne	C	91		e
---------- *C*-(*p*-Methoxyphenyl)-*N*-phenylnitrone ----------				
Benzyne	C	14		e
---------- *C*-(5-Nitro-2-furyl)-*N*-phenylnitrone ----------				
Propargyl bromide	P	3	E	ww
Progaryl alcohol	P	3	E	ww
---------- *C*-(6-Uracilyl)-*N*-phenylnitrone ----------				
Propargyl alcohol	G	62		vv
Propargyl bromide			O	vv

1. A 5-Substituted isoxazolidine or 5-substituted isoxazoline.
   B 4-Substituted isoxazolidine or 4-substituted isoxazoline.
   C Isoxazolidine or isoxazoline.
   G Structure of adduct not known or not reported.
   P Product not isolated as cycloadduct.
2. A legend for Tables III-IX is given after Table IX.
3. References are given after Table IX.

TABLE IV

1,3-CYCLOADDITION REACTIONS OF NITRONES WITH CONJUGATED ALKENES AND ALKYNES

Alkene or Alkyne	Adduct[1]	Yield,%[2]	Remarks[2]	Ref.[3]
Alkenes				
---------- N-t-Butylnitrone ----------				
Styrene	A	73		a
α-Methylstyrene	A	72		a
trans-β-Methylstyrene	A	46		a
---------- N-1-Ethylcyclohexylnitrone ----------				
Styrene	A	95		cc
---------- N-Methylenebicyclohexyl-1-ylamine N-oxide ----------				
Styrene	A	H		cc
---------- N-1-Ethylcyclopentylnitrone ----------				
Styrene	A	H		cc
---------- N-1,1,3,3-Tetramethylbutylnitrone ----------				
Styrene	A	H		cc
---------- C-Phenyl-N-methylnitrone ----------				
α-Methylstyrene	A	85	I	i,l
1,1-Diphenylethene	A	63		i,l
2-Vinylpyridine	A	100		i
Indene	A	92	J	i,l
1,2-Dihydronaphthalene	A	97	J	i,l
Acenaphthylene	C	78		i
Styrene	A	95	I	j,l

(Continued)

TABLE IV (Continued)

3,4-Dihydroisoquinoline N-oxide				
1,1-Diphenylethene	A	86		i
Indene	A	70	J	i
Styrene	A	82	I	j
C-(4-Chlorophenyl)-N-methylnitrone				
Styrene	A	99	I	j
C-(p-X phenyl)-N-phenylnitrone (X = H, Cl)				
p-X benzylideneacenaphthenones (X = H, Cl)	C	32-48	E	y
C-(X-phenyl)-N-phenylnitrone (X = H, o-NO_2, m-NO_2, p-NO_2)				
Styrene	A	H	I	bb
1,1-Diphenylethene	A	H	I	bb
C,N-Diphenylnitrone				
α-Methylstyrene	A	70	D,I	i
1,1-Diphenylethene	A	78		i
Acenaphthylene	C	94	I	i
Styrene	A	79	I	j,l
trans-stilbene	C	H	I	bb
C,C,N-Triphenylnitrone				
Styrene	A	86	I	j
C-Benzoyl-N-phenylnitrone				
Styrene	A	73	J	b
α-Methylstyrene	A	85	I	b
Indene	A	74	J	b
Acenapthylene	C	71		b

(Continued)

TABLE IV (Continued)

C-(p-Nitrobenzoyl)-N-phenylnitrone				
Styrene	A	99	J	b
C-(5-Nitro-2-furyl)-N-phenylnitrone				
Styrene	A	98		ww
4-Vinylpyridine	A	88		ww
trans-Stilbene	C	10		ww
C-(6-Uracilyl)-N-phenylnitrone				
Styrene	A	100		vv
1-Vinylpyridine	A	100		vv
trans-Stilbene			O	vv
C-Methyl-N-phenylnitrone				
Styrene	A	66	I,N	j
C-Propyl-N-cyclohexylnitrone				
Styrene	A	98	I,N	j
C-Propyl-N-phenylnitrone				
Acenaphthylene	C	73	J,N	i
Styrene	A	99	I,N	j,l
Cis- and trans-$R_1HC{=}N(O)R_2$ (R_1 = CN, R_2 = OCH_3)				
p-Methylstyrene	A	H	I	m
Alkynes				
N-t-Butylnitrone				
Phenylacetylene	A	80		a
C-(5-Nitro-2-furyl)-N-phenylnitrone				
Phenylacetylene	P	13	E	ww

(Continued)

TABLE IV (Continued)

---------- C-(6-Uracilyl)-N-phenylnitrone ----------			
Phenylacetylene	A	61	vv

1. A 5-Substituted isoxazolidine or 5-substituted isoxazoline.
   B 4-Substituted isoxazolidine or 4-substituted isoxazoline.
   C Isoxazolidine or isoxazoline.
   G Structure of adduct not known or not reported.
   P Product not isolated as cycloadduct.
2. A legend for Tables III-IX is given after Table IX.
3. References are given after Table IX.

TABLE V

1,3-CYCLOADDITION REACTIONS OF NITRONES WITH
α,β-UNSATURATED CARBONYL COMPOUNDS

Alkene or Alkyne	Adduct[1]	Yield, %[2]	Remarks[2]	Ref.[3]
Alkenes				
---------- N-t-Butylnitrone ----------				
Methyl acrylate	A	78		a
Methyl methacrylate	A	58		a
trans-Crotonaldehyde		49		a
	A	53		
	B	47		
trans-Methyl crotonate		67		a
	A	40		
	B	60		
trans-Methyl cinnamate		89		a
	A	31		
	B	69		
---------- CH_2NHO (The Parent Nitrone) ----------				
Methyl acrylate	A	Q	N	dd
Acrylonitrile	A	Q	N	dd
Methyl methacrylate	A	Q	N	dd
Methyl fumarate	C	Q	N	dd
Methyl maleate	C	Q	N	dd
---------- N-1-Ethylcyclohexylnitrone ----------				
Maleic anhydride	C	H		cc

(Continued)

TABLE V (Continued)

---------- C-Phenyl-N-methylnitrone ----------				
Dimethyl maleate	C	91	I	g
Dimethyl fumarate	C	H	I	g
cis-1,2-Dibenzoylethylene	C	81	I	g
trans-1,2-Dibenzoylethylene	C	85	I	g
Methyl citraconate	C	86	I	g
Methyl mesaconate	C	100	I	g
Ethyl acrylate	A	99	J	h,l
Methyl methacrylate	A	97	I	h
Ethyl Crotonate	B	95	J	h,l
Ethyl β,β-dimethylacrylate	B	81	J	h
Carvone	C	85	J,K	h,l
Eucarvone	C	68	J,K	h,l
Mesityl oxide	B	26	J	h,l
---------- 3,4-Dihydroisoquinoline N-oxide ----------				
Dimethyl fumarate	C	100	I	g
Dimethyl maleate	C	95	I	g
Maleic anhydride	C	86	I	g
N-Phenylmaleimide	C	82	I	g
Ethyl acrylate (Methyl acrylate)	A	99	J	h
Methyl methacrylate	A	100	I	h
Ethyl β,β-dimethylacrylate	B	93	J	h
---------- C,C-Diphenyl-N-methylnitrone ----------				
α,β-Unsaturated ketones	A	H		ee

(Continued)

TABLE V (Continued)

C,N-Diphenylnitrone				
Maleic anhydride	C	49	I	g
N-Phenylmaleimide	C	100	I	g
trans-Dibenzoylethylene	C	100	I	g
Ethyl acrylate	A	100	I	h
Methyl methacrylate	A	97	I	h
Ethyl crotonate (Methyl crotonate)	B	93	J	h
Ethyl p-nitrocinnamate	B	90	J	h
Methyl β,β-dimethylacrylate (Ethyl β,β-dimethylacrylate)	B	97	J	h
Ethyl crotonate	B	H		bb
C-(X-substituted)-N-phenylnitrones (X = 2-furyl, phenyl, 2-thienyl)				
N-Phenylmaleimide	C	H	E,I	s
C-(p-R_1 phenyl)-N-(p-R_2 phenyl) nitrone (R_1 = H, NO_2, OCH_3; R_2 = H, CH_3, t-butyl, Cl)				
N-(p-R_3 phenyl)maleimides (R_3 = H, NO_2, OCH_3)	C	H	E,I	s
C-Benzoyl-N-phenylnitrone				
Acrylic acid	A	76	J	b
Methyl acrylate	A	100	J	b
Methyl methacrylate	A	96	J	b
Methyl crotonate	B	92	J	b
Dimethyl fumarate	C	70	J	b
Dimethyl maleate	C	99	J	b
N-Phenylmaleimide	C	92	J	b
trans-Dibenzoylethylene	C	85	J	b

(Continued)

TABLE V (Continued)

---------- C-(p-Nitrobenzoyl)-N-phenylnitrone ----------				
Methyl acrylate	A	100	J	b
Dimethyl fumarate	C	89	J	b
---------- C,C-Diphenylnitrone ----------				
α,β-Unsaturated ketones	A	H	N	ee
---------- C,C,N-Triphenylnitrone ----------				
Dimethyl maleate	C	54	I	g
Dimethyl fumarate	C	64	I	g
Ethyl crotonate	B	80		h
---------- C-(5-Nitro-2-furyl)-N-phenylnitrone ----------				
Acrylamide	A	77		ww
---------- C-(6-Uracilyl)-N-phenylnitrone ----------				
Methyl acrylate	A	100		vv
Acrylamide	A	100		vv
Methyl methacrylate	A	86		vv
Ethyl cinnamate			O	vv
Maleic anhydride			O	vv
---------- C-Methyl-N-ethylnitrone ----------				
Methyl methacrylate	B	75	I,N	jj
---------- C-(n-Propyl)-N-Cyclohexylnitrone ----------				
Methyl acrylate	A	85	J	h
Methyl methacrylate	A	96	J	h,l
---------- C-(n-Propyl)-N-phenylnitrone ----------				
N-Phenylmaleimide	C	95	N,I	g
Ethyl acrylate	A	96	J	h

(Continued)

TABLE V (Continued)

Δ^1-Pyrroline N-oxide				
Ethyl crotonate	B	79	J	h
5,5-Dimethyl-Δ^1-pyrroline N-oxide				
Methyl methacrylate	A	Q		gg
Ethyl crotonate	B	Q		gg
Methyl cinnamate	B	Q		gg
Acrylamide	A	Q		gg
N-t-Butylacrylamide	A	Q		gg
Mesityl oxide	B	Q		gg
2-Cyclohexenone	B	H		gg
Ethyl acrylate	A(25°)	100		hh
	B(100°)	98		hh
Ethyl acrylate	A	H		mm
2,4,4-Trimethyl-Δ^1-pyrroline N-oxide				
Ethyl acrylate	C	Q	F	hh
3,3,5,5-Tetramethyl-Δ^1-pyrroline N-oxide				
Ethyl acrylate	C	Q	F	hh
Ethyl acrylate	A	H		mm
Cis- and trans-$R_1HC{=}N(O)R_2$ (R_1 = CN, CO_2CH_3, p-$NO_2C_6H_4$; R_2 = OCH_3, OC_2H_5)				
Methyl acrylate	A	H	I	m
1-Butene-3-one	A	H	I	m
N-Methylmaleimide	C	H	I	m
Dimethyl fumarate	C	H	I	m
Maleic anhydride	C	H	I	m

(Continued)

TABLE V (Continued)

Alkynes

---------- N-t-Butylnitrone ----------				
Ethyl propiolate		71		a
	A	70		
	B	30		
Dimethyl acetylenedicarboxylate	C	H		cc
3-Methylbutyn-3-ol	C	H		cc
---------- CH_2NHO (The Parent Nitrone) ----------				
Ethyl propiolate	P	Q	E,N	dd
---------- N-(2,4,6-Trimethylphenyl)nitrone ----------				
Dimethyl acetylenedicarboxylate	P	H		cc
---------- C-Phenyl-N-methylnitrone ----------				
Methyl propiolate		92		e
	A	42		
	B	58		
---------- 3,4-Dihydroisoquinoline N-oxide ----------				
Methyl propiolate	B	83		e
Ethyl phenylpropiolate	C	69		e
Dimethyl acetylenedicarboxylate	P	39	E	e
---------- C-(6-Uracilyl)-N-phenylnitrone ----------				
Dimethyl acetylenedicarboxylate			O	vv
Ethyl phenylpropiolate			O	vv

(Continued)

TABLE V (Continued)

1. A 5-Substituted isoxazolidine or 5-substituted isoxazoline.
   B 4-Substituted isoxazolidine or 4-substituted isoxazoline.
   C Isoxazolidine or isoxazoline.
   G Structure of adduct not known or not reported.
   P Product not isolated as cycloadduct.

2. A legend for Tables III-IX is given after Table IX.

3. References are given after Table IX.

TABLE VI

1,3-CYCLOADDITION REACTIONS OF NITRONES WITH DIENES, TRIENES, AND TETRAENES

Diene, Triene, or Tetraene	Adduct[1]	Yield, %[2]	Remarks[2]	Ref.[3]
Dienes				
---------- N-Methylnitrone ----------				
2,3-Dimethyl-1,3-butadiene	G	H	F,K,N	11
---------- N-Ethylnitrone ----------				
2,3-Dimethyl-1,3-butadiene	G	H	D,N	kk
---------- N-1-Ethylcyclohexylnitrone ----------				
Dicyclopentadiene	G	H		cc
---------- C-Phenyl-N-methylnitrone ----------				
Norbornadiene	C	91	J,K	k,l
Norbornadiene	C	2	J,L	k,l
---------- 3,4-Dihydroisoquinoline N-oxide ----------				
Norbornadiene	C	39	J,K	k
Cyclopentadiene	G	H	K	kk
2,3-Dimethyl-1,3-butadiene	G	H	F,K	11
---------- C,N-Diphenylnitrone ----------				
Dicyclopentadiene	C	72	I	k
Norbornadiene	C	54	J,K	k
Norbornadiene	C	3	J,L	k
Norbornadiene	C	82	I	aa
---------- C-Benzoyl-N-phenylnitrone ----------				
1,3-Butadiene	A	100	J,K	b

(Continued)

TABLE VI (Continued)

---------- C-(5-Nitro-2-furyl)-N-phenylnitrone ----------				
Isoprene	A	95	D,K	ww
Dicyclopentadiene	C	66	D,K	ww
Cyclooctadiene	C	61		ww
---------- C-(n-propyl)-N-cyclohexylnitrone ----------				
Norbornadiene	C	79	J,K	k
---------- 4,5,5-Trimethyl-Δ^1-pyrroline N-oxide ----------				
Isoprene	G	H	K	kk
trans,trans-Diethyl muconate	G	H	L	kk
2,3-Dimethyl-1,3-butadiene	G	H	F,K	11
Cyclopentadiene	G	H	F,K	11
---------- 2,3,4,5-Tetrahydropyridine N-oxide ----------				
2,3-Dimethyl-1,3-butadiene	G	H	D,F	kk,11
1,4-Diphenyl-1,3-butadiene	G	H	L	kk
1,3-Butadiene	G	H	D,F	11
Isoprene	G	H	F,K	11
Cyclopentadiene	G	62	F,K	11
Trienes				
---------- N-t-Butylnitrone ----------				
6,6-Dimethylfulvene	C	54	K	a
	C	21	L	
6,6-Diphenylfulvene	C	67	K	a
	C	14	K	
	C	11	L	
6-Methyl-6-phenylnitrone	C	67	K	a
	C	28	L	

(Continued)

TABLE VI (Continued)

---------- C-Phenyl-N-Methylnitrone ----------				
6,6-Dimethylfulvene	G	H	D	a
6,6-Diphenylfulvene	C	H	K	a
Cycloheptatriene		83	D	1
Tetraenes				
---------- 3,4-Dihydroisoquinoline N-oxide ----------				
---------- C-Phenyl-N-methylnitrone ----------				
---------- C,N-Diphenylnitrone ----------				
---------- C-Phenyl-N-(p-chlorophenyl)-nitrone ----------				
---------- C,C,N-Triphenylnitrone ----------				
Cyclooctatetraene (and its derivatives)			E	r

1. A 5-Substituted isoxazolidine or 5-substituted isoxazoline.
   B 4-Substituted isoxazolidine or 4-substituted isoxazoline.
   C Isoxazolidine or isoxazoline.
   G Structure of adduct not known or not reported.
   P Product not isolated as cycloadduct.
2. A legend for Tables III-IX is given after Table IX.
3. References are given after Table IX.

TABLE VII

1,3-CYCLOADDITION REACTIONS OF NITRONES WITH COMPOUNDS CONTAINING CUMULATED BONDS

Dipolarophile	Adduct[1]	Yield, %[2]	Remarks[2]	Ref.[3]
---------- N-t-Butylnitrone ----------				
Phenyl isocyanate	M	82		a
---------- N-1-Ethylcyclohexylnitrone ----------				
Phenyl isocyanate	M	90		cc
α-Naphthyl isocyanate	M	H		cc
Carbon disulfide	P	H	E	cc
---------- N-Methylenebicyclohexyl-1-ylamine N-oxide ----------				
Phenyl isocyanate	M	98		cc
---------- N-1-Ethylcyclopentylnitrone ----------				
Phenyl isocyanate	M	96		cc
---------- C-Phenyl-N-methylnitrone ----------				
Phenyl isocyanate	M	94		c,l
Phenyl isothiocyanate	P	52	E	c,l
---------- 3,4-Dihydroisoquinoline N-oxide ----------				
Phenyl isocyanate	M	96		c
---------- C-Phenyl-N-(t-butyl)nitrone ----------				
Carbon disulfide	G,P			v
---------- $R_1R_2C{=}N(O)R_3$ ----------				
R_1 / R_2 / R_3				
Ph / H / t-Bu				
Ph / H / Me				
Ph / H / Ph				
$-(CH_2)_5-$ / Me				
Diphenylcarbodiimide			E	nn

(Continued)

TABLE VII (Continued)

N-Fluorenylidenealkylamine N-oxide (alkyl = Me, Et, i-Pr)				
Diphenylketene			E	qq
C,N-Diphenylnitrone				
Carbon disulfide	P		E	v
Phenyl isocyanate	M	80		c
x-phenyl isocyanate (x = H, p-CH_3, p-OCH_3, p-OC_2H_5, p-Cl, m-Cl, m-NO_2)	M	88-94		xx
Eynes	A	12-50	K	ii
Dimethylketene			E	rr,uu
C-(X-phenyl)-N-phenylnitrone (X = p-NO_2, m-NO_2, m-Cl, p-Cl, p-OCH_3, p-OCH_2Ph, p-NMe_2, p-NEt_2)				
Phenyl isocyanate	M	57-98		xx
C-Phenyl-N-(o-toyl)nitrone				
Dimethylketene			E	uu
C-Benzoyl-N-phenylnitrone				
"Diketene"			E	pp
Dimethylketene			E	rr
C-Benzoyl-N-(2,6-xylyl)nitrone				
Dimethylketene			E	ss
C-(6-Uracilyl)-N-phenylnitrone				
Phenyl isocyanate	M	H		vv
Carbon disulfide		10	E	vv
Phenyl isothiocyanate	G	H		vv
Benzoyl isocyanate	G	H		vv
Benzoyl isothiocyanate	G	H		vv

(Continued)

TABLE VII (Continued)

---------- C-(5-Nitro-2-furyl)-N-phenylnitrone ----------				
Carbon disulfide	P	61	E	ww
Dicyclohexylcarbodiimide	P	18	E	ww
Phenyl isocyanate	P	33	E	ww
---------- 5,5-Dimethyl-Δ^1-pyrroline N-oxide ----------				
Carbon disulfide	P		E	v
---------- 4-Phenyl-5,5-dimethyl-Δ^1-pyrroline N-oxide ----------				
Carbon disulfide	P		E	v
---------- 3,3,5,5-Tetramethyl-Δ^1-pyrroline N-oxide ----------				
Carbon disulfide	P	E		v
---------- Quinoxalin-3(4H)-one 1-N-oxides ----------				
Aryl isocyanates			E,P	oo

1. A 5-Substituted isoxazolidine or 5-substituted isoxazoline.
   B 4-Substituted isoxazolidine or 4-substituted isoxazoline.
   C Isoxazolidine or isoxazoline.
   G Structure of adduct not known or not reported.
   P Product not isolated as cycloadduct.
2. A legend for Tables III-IX is given after Table IX.
3. References are given after Table IX.

TABLE VIII

1,3-CYCLOADDITION REACTIONS OF NITRONES WITH MISCELLANEOUS UNSATURATED COMPOUNDS

Dipolarophile	Adduct[1]	Yield, %[2]	Remarks[2]	Ref.[3]
Alkenes				
---------- N-t-Butylnitrone ----------				
Nitroethylene	A	H		a
Acrylonitrile	A	72		a
1-Acetoxy-1-cyanoethylene	A	79		a
α-Methylacrylonitrile	A	72		a
1-N-Morpholino-1-cyclohexene	G	Q		a
Phenyl vinyl sulfone		98		a
	A	70		
	B	30		
Phenyl vinyl sulfide	A	96		a
iso-Butyl vinyl ether	A	61		a
Vinyl acetate	A	46		a
iso-Propenyl acetate			O	a
Vinylidene cyanide			O	a
---------- C-Phenyl-N-methylnitrone ----------				
Nitroethylene	B	76	I	a
Phenyl vinyl sulfone		86		a
	A	32	I	
	B	68	I	
Acrylonitrile	A	91	I	h,l
n-Butyl vinyl ether	A	83	J	i

(Continued)

TABLE VIII (Continued)

C-Phenyl-N-methylnitrone (Continued)				
Dihydropyran	G	H		l
Fumaronitrile	C	76	l	g
3,4-Dihydroisoquinoline N-oxide				
1,1-Diethoxyethene	A	98		i
C,N-Diphenylnitrone				
Acrylonitrile	A	100	I	h
1,1-Diethoxyethene	A	98		h
1-N-Pyrrolidino-1-phenylethylene	A	48	J	p
1-N-Morpholino-1-cyclohexene	P	7	E	p
1-N-Piperidino-1-cyclohexene	P	9	E	p
1-N-Pyrrolidino-1-cyclohexene	A	60	I	p,q
1-N-Morpholino-1-cyclohexene	A	7		q
C-(p-Chlorophenyl)-N-phenylnitrone				
1-Pyrrolidino-cis-3,5-dimethylcyclohexene	B	27	J	o
1-N-Pyrrolidino-1-phenylethylene	A	62	J	p
1-N-Morpholino-1-cyclohexene	A	3	J	p
1-N-Pyrrolidino-1-cyclohexene	A	69	D,I	p
C-(p-Methoxyphenyl)-N-phenylnitrone				
1-N-Pyrrolidino-1-cyclohexene	A	50	I	p
C-(m-Nitrophenyl)-N-phenylnitrone				
1-Pyrrolidino-cis-3,5-dimethylcyclohexene	B	66	J	o
C-(p-Nitrophenyl)-N-phenylnitrone				
1-N-Pyrrolidino-1-phenylethylene	A	49	J	p
1-N-Pyrrolidino-1-cyclohexene	A	60	I	p

(Continued)

TABLE VIII (Continued)

C-(X-phenyl)-N-phenylnitrone (X = H, o-NO_2, m-NO_2, p-NO_2)				
Vinyl acetate	A	H	I	bb
C-Benzoyl-N-phenylnitrone				
Acrylonitrile	A	85	J	b
C-(p-Nitrobenzoyl)-N-phenylnitrone				
Acrylonitrile	A	75	I	b
C-(6-Uracilyl)-N-phenylnitrone				
1-N-Morpholino-1-cyclohexene	A	H		vv
C-(n-propyl)-N-phenylnitrone				
α,β-Unsaturated oximes and unsaturated O-ethers of oximes	A	H		z
5,5-Dimethyl-Δ^1-pyrroline N-oxide				
Acrylonitrile	A	100		hh
Crotononitrile	G	H		11
Cis- and trans-$R_1HC{=}N(O)R_2$ (R_1 = CN, R_2 = OCH_3)				
Acrylonitrile	A	H	I	m
Alkynes				
N-t-Butylnitrone				
Cyanoacetylene		58		a
	A	50		
	B	50		
C-Phenyl-N-methylnitrone				
Cyanoacetylene	B	82		a
C,N-Diphenylnitrone				
Cyanoacetylene	G	H	D	a

(Continued)

TABLE VIII (Continued)

C-(6-Uracilyl)-N-phenylnitrone				
Cyanoacetylene	G	48		vv
Chlorocyanoacetylene			O	vv
Other Compounds				
C-Phenyl-N-methylnitrone				
Methylenetriphenylphosphorane		17	E	f
3,4-Dihydroisoquinoline N-oxide				
Methylenetriphenylphosphorane		74	E	f
Benzylidenetriphenylphosphorane		81	E,J	f
C,N-Diphenylnitrone				
Methylenetriphenylphosphorane		93	E	f
Benzylidenetriphenylphosphorane		39	E,J	f
Isopropylidenetriphenylphosphorane		22	E	f
5,5-Dimethyl-Δ^1-pyrroline N-oxide				
Aziridinium salts			E	x
2,5,5-Trimethyl-Δ^1-pyrroline N-oxide				
Paraformaldehyde	P	Q	E	hh

1. A 5-Substituted isoxazolidine or 5-substituted isoxazoline.
   B 4-Substituted isoxazolidine or 4-substituted isoxazoline.
   C Isoxazolidine or isoxazoline.
   G Structure of adduct not known or not reported.
   P Product not isolated as cycloadduct.
2. A legend for Tables III-IX is given after Table IX.
3. References are given after Table IX.

TABLE IX

REACTIONS OF HETEROAROMATIC N-OXIDES

Heteroaromatic	Adduct[1]	Yield, %[2]	Remarks[2]	Ref.[3]
---------- Dibenzoylfuroxan ----------				
Styrene	P	35		u
Phenylacetylene	P	70		u
---------- Isoquinoline N-oxide ----------				
Phenyl isocyanate	M	75	P	c
Phenyl isothiocyanate	P	59	E	c
Carbon disulfide	P	95	E	c
Methyl propiolate (Ethyl propiolate)	P	70	E	d
Dimethyl acetylenedicarboxylate (Diethyl acetylenedicarboxylate)	P	77	E	d
Methyl phenylpropiolate	P	49	E	d
Dimethylketene			E	tt
---------- 2-Methyl-4-phenyl-quinozoline 3-oxide ----------				
Dimethyl acetylenedicarboxylate (Diethyl acetylenedicarboxylate)			E,D	t
---------- Phenanthridine N-oxide ----------				
Ethyl acrylate	A	66	P	d
Phenyl isocyanate	M	87	P	c
Dimethyl acetylenedicarboxylate	P	96	E	d
Dimethylketene			E	tt
---------- Phenanthridine N-oxides ----------				
Dimethyl acetylenedicarboxylate and other acetylenic esters	P		E	ff

(Continued)

TABLE IX (Continued)

---------- 2-Phenylisotagen ----------				
Styrene	A	81	J	b
Ethyl acrylate	A	93	J	b
Diethyl fumarate	C	86	J	b
Cyclopentene	C	65	J	b
Norbornene	C	81	J	b
Butyl vinyl ether	A	42	J	b
Methyl phenylpropiolate	C	74		e
---------- Pyridine N-oxide ----------				
Phenyl isocyanate	M	77	P	c
Dimethylketene			E	tt

1. A 5-Substituted isoxazolidine or 5-substituted isoxazoline.
   B 4-Substituted isoxazolidine or 4-substituted isoxazoline.
   C Isoxazolidine or isoxazoline.
   G Structure of adduct not known or not reported.
   P Product not isolated as cycloadduct.
2. A legend for Tables III-IX is given after Table IX.
3. References are given after Table IX.

LEGEND FOR TABLES III-IX

A 5-Substituted isoxazolidine or 5-substituted isoxazoline.

B 4-Substituted isoxazolidine or 4-substituted isoxazoline.

C Isoxazolidine or isoxazoline.

D Mixture of products.

E Structure of product(s) reported, but not as A, B, or C.

F Structure of adduct assumed or not rigorously established.

G Structure of product not known or not reported.

H Not specified.

I Stereochemistry of adduct reported, or adduct identified as a mixture of diasteromers.

J Stereochemistry of adduct not known or not reported.

K 1:1 Adduct.

L 2:1 Adduct.

M 1,2,4-oxadiazolidin-5-one.

N Nitrone generated <u>in situ</u>.

O No reaction.

P Product not isolated as cycloadduct.

Q Yield given, but not as % yield.

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II A. PERTURBATION TREATMENT OF CYCLOADDITIONS

1. Frontier Orbital Concepts

Perturbation theory is a powerful tool for the understanding of diverse organic phenomena.[38] Early treatments of cycloaddition reactions by perturbation theory resulted in the landmark orbital symmetry selection rules for concerted cycloadditions. Houk *et al.*,[10] have recently applied perturbation theory to rationalize and reveal the origin of reactivity, regioselectivity, and periselectivity in 1,3-dipolar cycloadditions. Applications of perturbation theory to cycloaddition reactions have recently been reviewed.[39]

The basic concepts of perturbation theory as they apply to 1,3-dipolar cycloaddition reactions are developed below. A more detailed and more quantitative discussion of the subject is given by Houk *et al.*[10] These studies were inspired by the predictions of perturbation theory, and the results obtained are compatible with the concepts of perturbation theory presented here. Experimental results of this research are given in Section II B.

Frontier orbitals for dipoles and dipolarophiles are defined as the highest occupied (HO) and lowest unoccupied (LU) molecular orbitals of each reactant. Interaction of the HO (E_1) molecular orbital of one polyolefin with the LU (E_2) molecular orbital of a second polyolefin is shown schematically in Figure 4. The interaction of the two orbitals results in depression of the energy of the lower energy orbital and raising of the energy of the higher energy orbital, and the extent of energy change, ΔE, is inversely proportional to the difference in

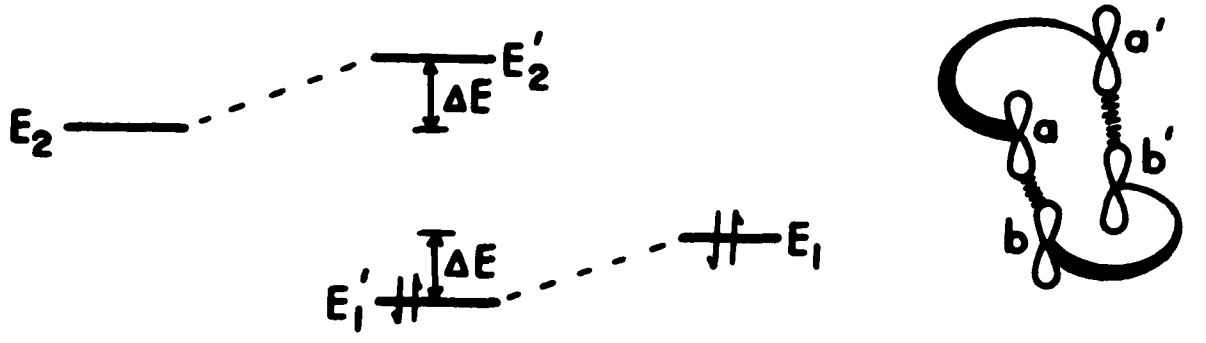


Figure 4. Schematic Representation of Orbital Mixing

energy (E_2 - E_1) of the orbitals prior to interaction.[38] Only interactions between the π orbitals of both reactants are considered since these orbitals will overlap most in the transition state of a cycloaddition. Most perturbation treatments of cycloaddition reactivity have focused only on interactions between the frontier orbitals of both reactants since the inverse dependence of stabilization energy, ΔE, on orbital energy differences insures that frontier orbital interactions are larger than other interactions; a schematic diagram is shown in Figure 5.

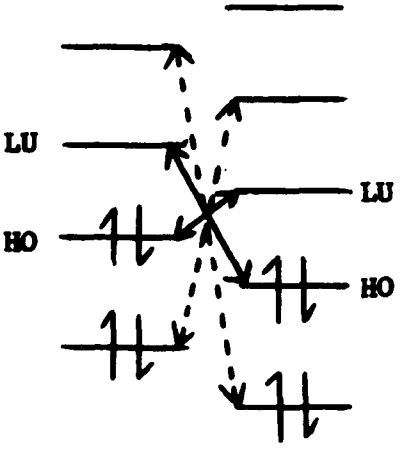


Figure 5. Schematic Representation of Orbital Interactions

In a 1,3-dipolar cycloaddition reaction involving an unsymmetrical 1,3-dipole and an unsymmetrical dipolarophile, two modes of approach of the dipole ($a^{\pm}b^{+}-c^{-}$) to the 2π electron dipolarophile (CH_2=CHR) are possible, as shown in Figure 6. In the early stages of

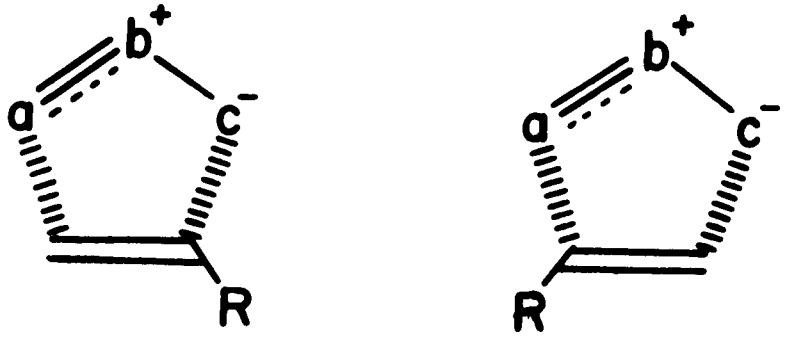


Figure 6. Modes of Approach of Addends in 1,3-Dipolar Cycloaddition Reactions

a cycloaddition reaction, when the interaction between two addends is small, perturbation theory is particularly suited for the estimation of the relative energies of different geometries of approach of the addends. Since most cycloadditions have low activation energies and large heats of reaction, the relative energies of different transition states should be paralleled by the relative energies of the corresponding weakly interacting complexes. If the assumption is made that entropies of activation will not differ significantly for the two isomeric transition states formed from a pair of addends (Figure 6), then the relative energies of the isomeric transition states can be approximated from perturbation theory. Although regioselectivity (selectivity in the direction of addition to an unsymmetrical dipolarophile) is the result of very small energy differences (0.1-5 kcal/mol) between two diastereomeric transition states, the estimation of such small energy differences is the forté of perturbation theory.[10]

By considering only frontier orbital interactions, the model used by Houk *et al.*,[10] is the same as that proposed by Sustmann,[40] who classified 1,3-dipolar cycloadditions into three types that depend upon the relative disposition of 1,3-dipole and dipolarophile frontier orbitals (Figure 7). The three types of interactions are referred to

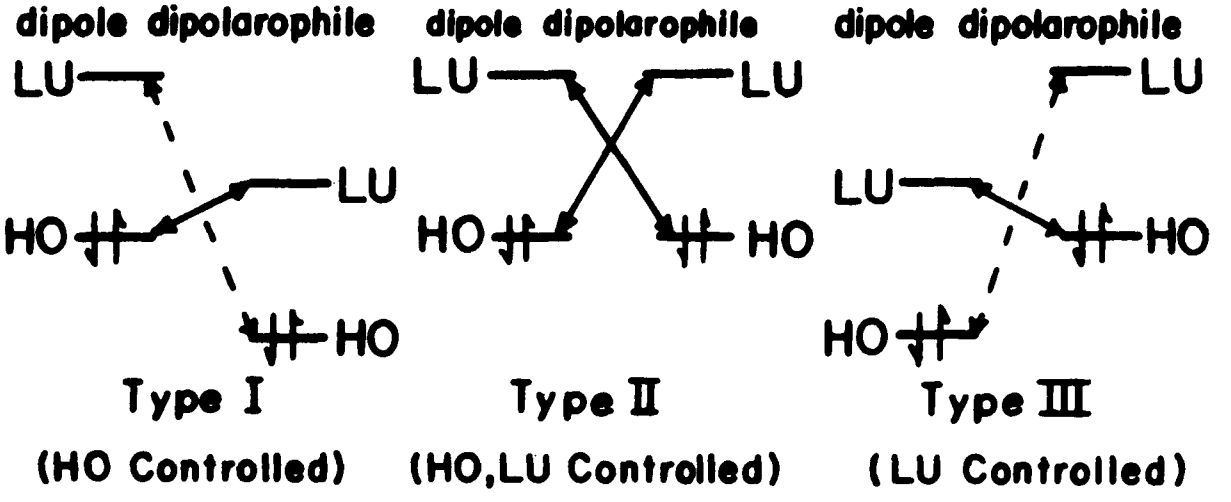


Figure 7. Sustmann's classifications of 1,3-Dipolar Cycloadditions

as HO controlled (the interaction of the dipole HO with the dipolarophile LU is greatest), HO, LU controlled (both frontier orbital interactions are large), and LU controlled (the interaction of the dipole LU with the dipolarophile HO is greatest). Sustmann has called these three limiting cases, Types I, II, and III, respectively.[40]

Reactivity in 1,3-dipolar cycloadditions reactions is related to the relative disposition of the interacting frontier orbitals that are shown in Figure 7. Frontier orbital interactions for Types I and III reactions are large, due to the small energy difference between interacting orbitals, and the rates of these kinds of reactions should be large. For LU, HO controlled cycloadditions (Type II), the frontier orbital interactions are smaller and reaction rates should be correspondingly smaller. The effects that substituents have on the dipole

and dipolarophile frontier orbitals are discussed in more detail later. Qualitatively, substituents which raise the dipole HO and LU energies, or lower the dipolarophile HO and LU energies will accelerate HO controlled reactions and decelerate LU controlled reactions. Conversely, substituents which lower the dipole HO and LU energies or raise the dipolarophile HO and LU energies will accelerate LU controlled reactions and decelerate HO controlled reactions. HO, LU controlled reactions will be accelerated by an increase of either frontier orbital interaction.[10]

Generalizations about the frontier molecular orbitals energies and coefficients of 1,3-dipoles and dipolarophiles are given below. These generalizations are subsequently used to account for relative reactivities, regioselectivity, and periselectivity (selective formation of one of several thermally allowed adducts) in nitrone cycloadditions.

2. Frontier Orbitals of 1,3-Dipoles

All 1,3-dipoles have in common a three atomic orbital system containing four electrons analogous to an allyl anion. A quantitative comparison of the allyl anion and two representative 1,3-dipoles is given in Figure 8. The allyl anion MO's were derived from CNDO/2 calculations in which 120° bond angles and a 1.40 Å C-C bond length were used, while in the case of formonitrile oxide (fulminic acid) calculations bond lengths obtained from optimization of the geometry (r_{CN} = 1.21 Å, r_{NO} = 1.22 Å) were used.[10] Calculations for the parent nitrone employed 120° bond angles and estimated bond lengths (r_{CN} = 1.32 Å; r_{NO} = 1.21 Å).[10] The sizes of the lobes of the 2 p orbitals in Figure 8 are roughly proportional to the coefficients obtained from these LCAO calculations, and energies are given in electron volts.

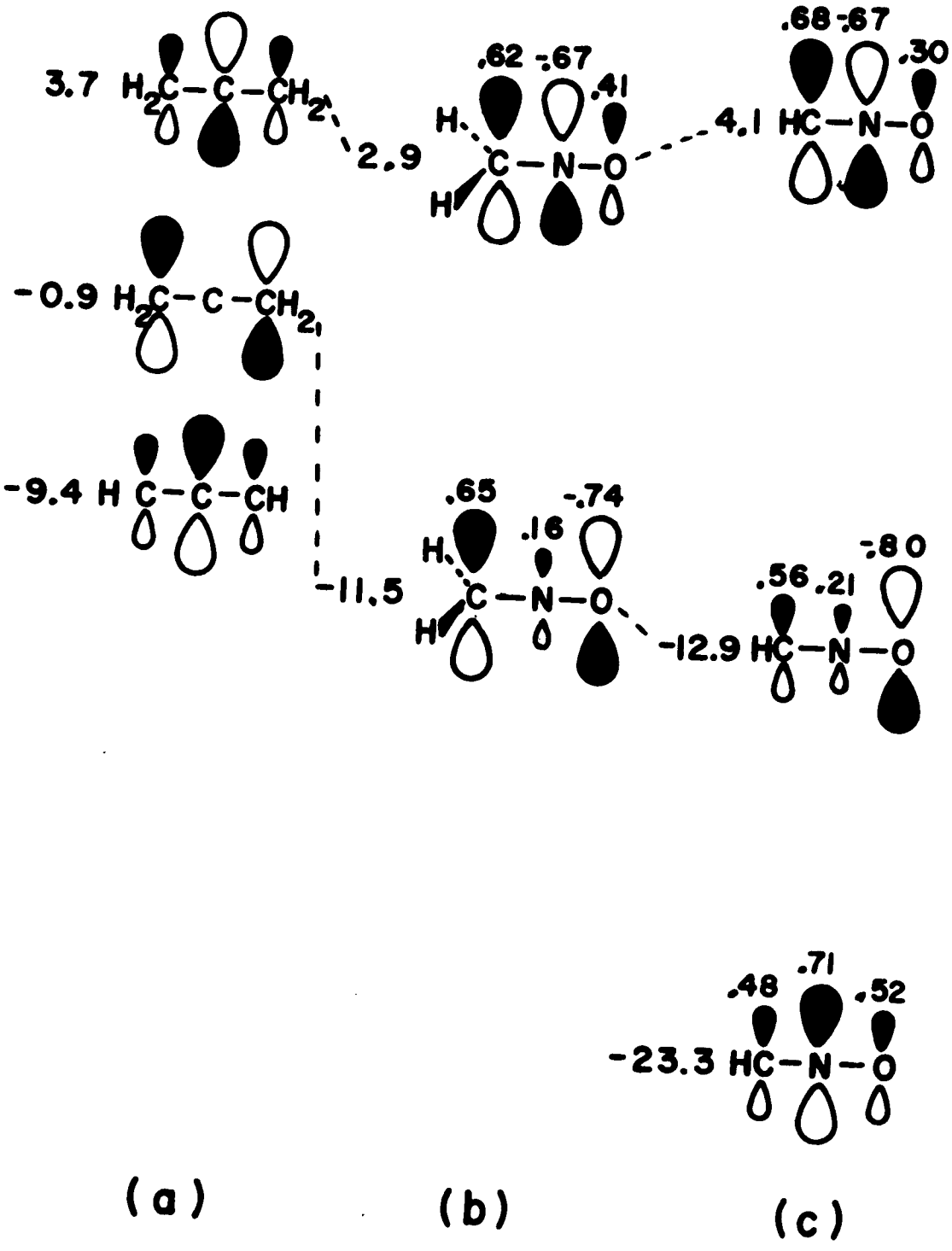


Figure 8. CNDO/2 π Orbitals of (a) Allyl Anion, (b) CH_2NO, the Parent Nitrone, and (c) Formonitrile Oxide

Although the approximate nodal properties of the allyl anion MO's are preserved in the dipoles, the absolute energies of the bonding orbitals are lowered considerably by the electronegative N and O atoms of the 1,3-dipoles. The allyl anion HO orbital has unusually high energy because of the charged nature of the anion. Formonitrile oxide has a LU orbital energy slightly higher than that of the allyl anion. This may be attributed to the shorter bond lengths and linearity of the nitrile oxide molecule which results in increased antibonding and decreased 1,3-bonding, respectively, as compared with the allyl anion.[10]

The relative sizes of the terminal coefficients of the HO and LU orbitals of formonitrile oxide are typical of most 1,3-dipoles. The larger coefficient is on the "anionic" terminus of the HO orbital and the "neutral" terminus of the LU molecular orbital. These differences in the magnitudes of the terminal coefficients in the HO and LU π orbital are, as discussed later, the source of regioselectivity in 1,3-dipolar cycloadditions. Calculations for the parent nitrone show that the terminal coefficients for the HO orbital are approximately equal while the larger terminal coefficient for the LU orbital, like other 1,3-dipoles, is on the neutral terminus (Figure 8).[10]

The relationship between reactivity and the frontier orbital energies of 1,3-dipoles has already been mentioned. Frontier orbital energies from experimental data or extrapolations from calculations for the common 1,3-dipoles are shown in Figure 9.[10] Since changes in the LU orbital energies parallel those of the HO orbital for any given series of 1,3-dipoles the energy of the HO orbital gives an indication of the reactivity of 1,3-dipoles. That is, when more electronegative atoms are present (cf. changing from an azomethine imine to a nitrone) both the HO and LU orbitals will decrease in energy and the dipole LU will tend to be increasingly important in controlling reactivity.

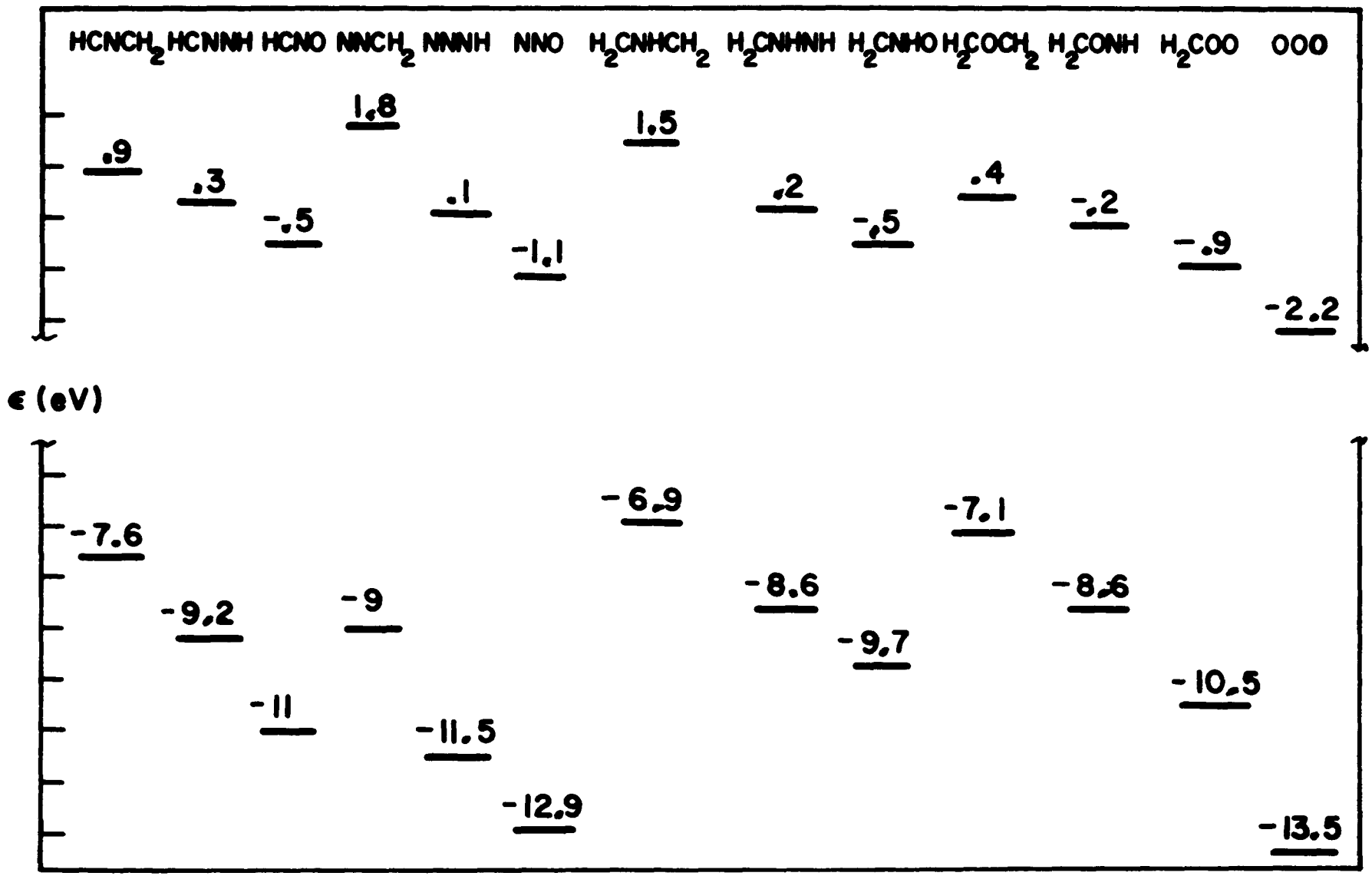


Figure 9. Estimated π Frontier Orbital Energies for the 1,3-Dipoles

Frontier orbital energies have been measured experimentally for some dipoles and dipolarophiles. The HO orbital energy of a molecule is defined as the negative of its ionization potential (-I.P.), and the LU orbital energy is defined as the negative of its electron affinity (-E.A.). Ionization potentials are readily accessible from photoelectron spectroscopic measurements, although so far, only a few 1,3-dipoles have been studied. The ionization potential of N-t-butylnitrone, for example, is 8.64 eV and its HO orbital energy is -8.64 eV. Electron affinities are, however, very difficult to measure and few electron affinities for dipoles and dipolarophiles are available in the literature. Consequently, LU orbital energies are almost entirely estimated from calculations and from ultraviolet spectral data.[10] Calculated and experimental frontier orbital energies show the same trends, if not the same absolute values, for a given series of dipoles or dipolarophiles.

3. Frontier orbitals of Dipolarophiles

Alkenes and Alkynes

Substituted ethylenes are conveniently divided into three broad classes: electron-rich ($CH_2CH\ddot{X}$ and CH_2CHR), electron-deficient (CH_2CHZ), and conjugated (CH_2CHC) alkenes. Qualitative conclusions about the frontier orbital energies and coefficients of ethylene and substituted ethylenes are given below.

The HO orbital energy of ethylene is -10.51 eV (i.e., I.P. = 10.51 eV) and the LU orbital energy is estimated to be 1.5 eV.[10] The orbital energies and coefficients of ethylene and the three classes of substituted ethylenes are shown in Figure 10. The generalized coefficient

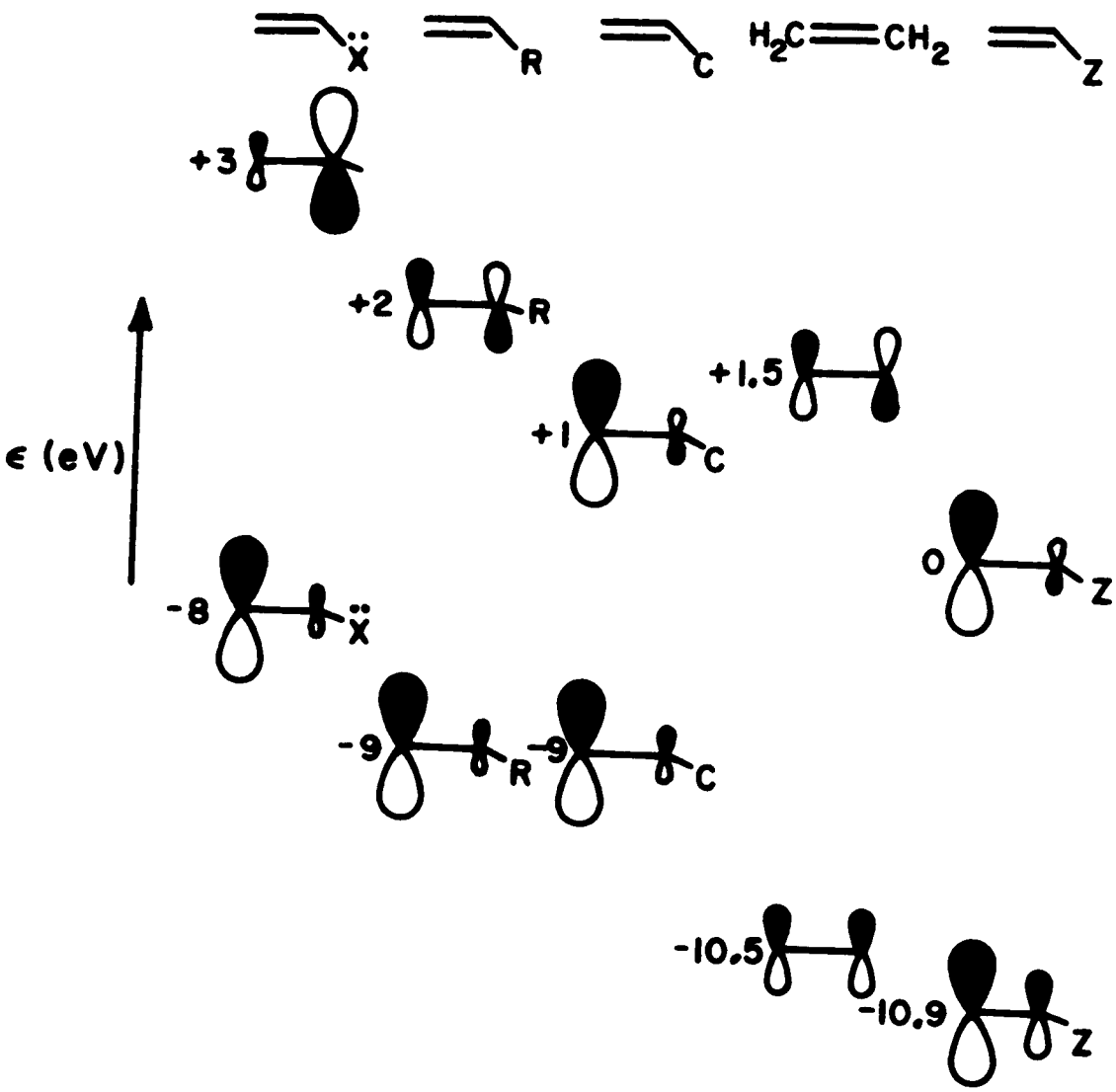


Figure 10. Estimated π Frontier Orbital Energies and Coefficients for Dipolarophiles

magnitudes were derived from CNDO/2 and EH calculations performed by Houk et al., and from calculations available in the literature.[10] The orbital energies are based on experimental values of π ionization potentials for compounds of a given class, and on measured or estimated electron affinities. Houk et al., have collected representative data from which these numbers are derived.[10]

Electron-rich alkenes are conveniently divided into two subclasses: the electron-rich alkylethylenes (CH_2CHR) and the very electron-rich alkenes such as enamines and enol ethers ($CH_2C\ddot{H}\ddot{X}$). Both types of alkenes have frontier orbitals which are raised in energy with respect to those of ethylene (Figure 10). The alkylethylenes generally have ionization potentials 1-2 eV lower than that of ethylene (i.e., higher HO orbital energies than ethylene) depending upon the type and number of alkyl substituents. The greater the number of alkyl substituents, the less the ionization potential and the higher the energy of the HO orbital. Propene, for example, has a π ionization potential of 9.73 eV, and 2-butene has a π ionization potential of 9.13 eV.[10] The LU orbital energies of alkylethylenes are estimated to change in the same direction as the HO orbital energies with alkyl substitution, but the changes in LU energies are smaller than the changes in HO energies. Trends in the destabilization of frontier orbital energies are similar, but more drastic for the very electron-rich alkenes which are substituted with more powerful electron donors such as alkoxy and amino groups.[10]

The size of the 2p orbitals in Figure 10 are roughly proportional to the calculated coefficients for representative members of each class of alkenes. The larger coefficient for the HO orbital of electron-rich alkenes is on the carbon removed from the substituent and

the larger coefficient for the LU orbital is on the carbon adjacent to the substituent. The LU coefficients for alkylethylenes are approximately equal in magnitude.[10]

Conjugating substituents raise the HO and lower the LU orbital energies of ethylene. The larger coefficient for the HO and LU orbitals is on the carbon removed from the substituent.[10]

Electron-withdrawing substituents which are simultaneously conjugating (-COR, -CN, etc.) lower the HO orbital energy of ethylene only slightly, but have a much larger lowering effect on the LU orbital energy. The larger coefficients for the HO and LU orbitals for these alkenes are on the carbon removed from the substituent.[10]

Other generalizations about frontier orbital coefficients can also be made. 1,2-Disubstituted ethylenes should have coefficients on both carbons which are more nearly equal in magnitude than those of monosubstituted alkenes. The two substituents of methyl trans-crotonate, for example, influence the magnitude of a given frontier orbital coefficient oppositely so that the frontier orbital coefficients of methyl trans-crotonate are more nearly equal than those of the monosubstituted alkene, methyl acrylate.[10]

The general characteristics of the frontier orbitals of alkenes and alkynes are similar. The HO orbital of an acetylene is lower in energy than the corresponding alkene, while the LU orbital of acetylene is slightly higher in energy than that of ethylene.[10]

The frontier orbitals of 1,3-dipoles were described earlier in this Section. Houk et al.,[10] have shown that electron-donating, conjugating, and electron-withdrawing substituents generally have the same effect on the frontier orbitals of 1,3-dipoles as they have on the

frontier orbitals of ethylene. The HO and LU orbital energies of C-phenyl-N-methylnitrone (5), for example, are higher and lower, respectively, than the corresponding frontier orbital energies of N-t-butylnitrone (13). Applications of these ideas are discussed in Section II B.

Fulvenes

Fulvenes are reactive (highly perturbed) trienes having only slightly differing steric requirements for different modes of reactions. The frontier π orbitals (relative energies and coefficients) of fulvene are shown schematically in Figure 11. This order of energies is found

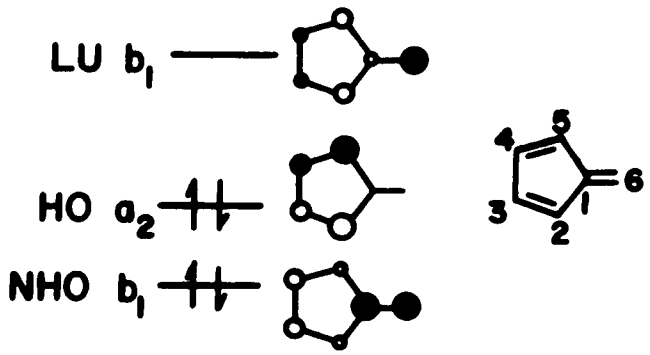


Figure 11. Frontier Orbitals of Fulvene

for the parent system by several methods of calculation.[41] Both calculations and ionization potentials from photoelectron spectroscopy show that the "NHO" (next to highest occupied) π orbital is destabilized more than the HO π orbital by substituents at the 6-position so that these two MO's have similar energies, perhaps in reversed order, in some fulvenes such as 6,6-diphenylfulvene. The energies of the HO and NHO orbitals of fulvene are similar to the energy of the HO orbital of a conjugated dipolarophile. The energies of the LU orbitals of fulvene, 6-conjugated, and 6,6-dialkyl fulvenes are similar to those of electron-deficient dipolarophiles

(Figure 10). Arguments about reactivity for reactions of 1,3-dipoles and fulvenes follow those given earlier in this Section for alkenes and alkynes.[41]

4. Reactivity, Regioselectivity, and Periselectivity

The frontier orbital explanation of reactivity for 1,3-dipolar cycloaddition has been discussed earlier in this Section in connection with the basic concepts of frontier orbital theory (page 59). Qualitatively, the preferred regioisomer in a 1,3-dipolar cycloaddition will be that one in which the atoms with the larger terminal coefficients in the most strongly interacting pair of frontier orbitals are united. This is shown schematically in Figure 12. Case (a) results in greater transition state stabilization than case (b). The reaction of nitrones,

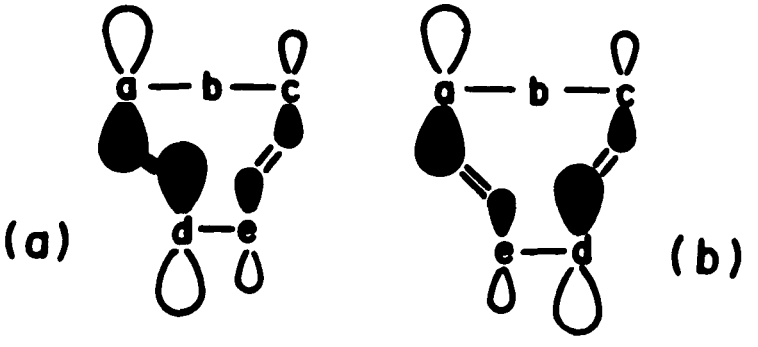


Figure 12. Schematic Representation of Greater Stabilization of Transition State (a) than (b) Due to Different Coefficient Magnitudes

for example, with electron-rich dipolarophiles are LU controlled reactions where the dominant frontier orbital interaction is between the dipole LU and the dipolarophile HO. Union of the larger terminal coefficients for this interaction will lead to the formation of the 5-substituted product with the dipolarophile substituent near the anionic terminus of the nitrone (Figures 8 and 10). Other examples are given in Section II B.

"Periselectivity" refers to the selective formation of one of several thermally allowed products in a cycloaddition reaction. The thermally allowed 1:1 cycloadducts of 1,3-dipoles and fulvenes are shown in Figure 1 (Section I A). For concerted cycloadditions of nitrones to fulvenes, the favored regioisomer and periisomer will be that in which the larger coefficients in each of the interacting frontier orbitals are united. That is, regioselectivity and periselecvivity are controlled by the same interactions. Applications of these ideas are discussed in Section II B.

PART B Reactions of Nitrones

1. Reactivity in Nitrone Cycloadditions

The frontier orbital energies for dipolarophiles, the parent nitrone (a tautomer of formaldoxime), C-phenyl-N-methylnitrone and N-t-butylnitrone are shown in Figure 13. These orbital energies are based on experimental data and/or calculations (Section II A).[10]

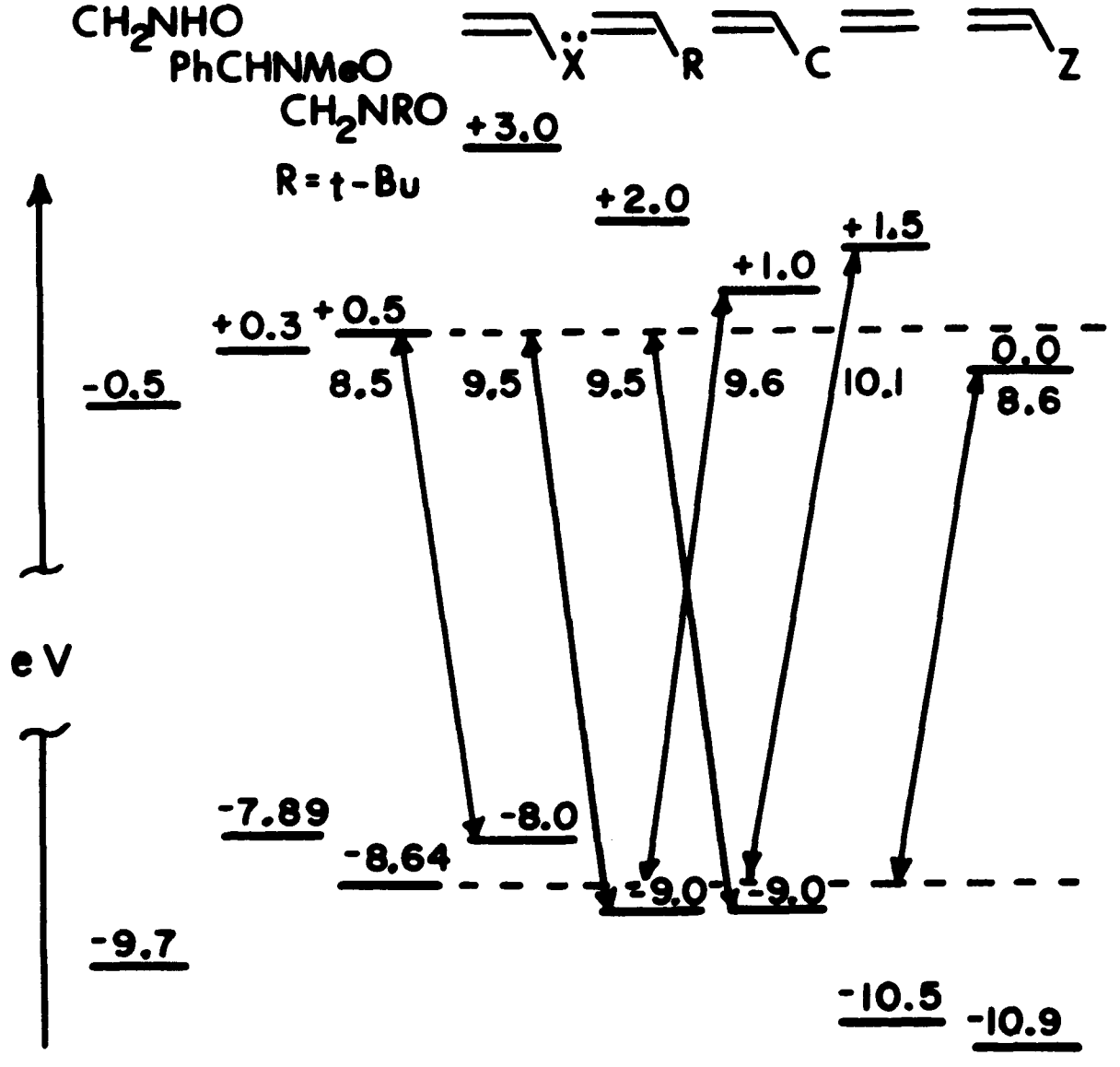


Figure 13. Frontier Orbital Energies of the Parent Nitrone, C-Phenyl-N-Methylnitrone, and Dipolarophiles

The reactions of N-t-butylnitrone with dipolarophiles may be grouped according to Sustmann's classifications (Section II A). A crossover from LU control for electron-rich dipolarophiles to HO control for electron-deficient dipolarophiles is expected. Reactions with electron-deficient dipolarophiles (CH=CHZ) are Type I (HO controlled) cycloadditions in which the dipole HO-dipolarophile LU interaction is dominant. The reactions with conjugated dipolarophiles (CH_2=CHC) are Type II (HO, LU controlled) cycloadditions in which both frontier orbital interactions are large. Finally, the reactions of N-t-butylnitrone with electron-rich dipolarophiles (CH_2=CH$\ddot{X}$ and CH_2=CHR) are Type III (LU controlled) cycloadditions in which the dipole LU-dipolarophile HO interaction is the greatest. The reactions of C-phenyl-N-methylnitrone can be classified in a similar way.

The reactivity and regioselectivity of nitrone cycloadditions can be rationalized by the data given in Figure 13. For both LU controlled reactions with very electron-rich dipolarophiles and HO controlled reactions with very electron-deficient dipolarophiles, the interaction of one frontier orbital of the nitrone with one frontier orbital of the dipolarophile is very large due to their small energy difference, and the rates of these kinds of reactions should be large. For LU, HO controlled cycloadditions of nitrones the frontier orbital interactions are smaller and reaction rates should be correspondingly smaller.

To verify these ideas, rate constants for the reaction of N-t-butylnitrone with a large number of dipolarophiles were measured. Reactions of equimolar quantities of reactants were carried out in sealed nmr tubes under nitrogen, and the disappearance of the nitrone was monitored by nmr spectroscopy.

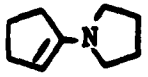
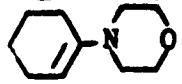
For a second-order reaction utilizing equal initial concentrations of reactants, the integrated form of the rate expression is $1/X - 1/A_O = kt$, and $k = 1/(A_O)t_{\frac{1}{2}}$, where k is the second order rate constant, A_O is the initial concentration of reactants, X is the concentration of one reactant at time t, and $t_{\frac{1}{2}}$ is the reaction half-life.[42] Half-lives were determined from plots of X *versus* t and 1/X *versus* t where the concentrations of the reactants were assumed to be directly proportional to the peak height of the methylene proton singlet of *N*-*t*-butylnitrone (6.0-7.0 ppm). The rate constants for four different reactions were determined from both peak height and integrated area data, and the rate constants for each reaction determined by the two methods differed by less than 10% from the average of the two values. Similarly, rate constants calculated from peak height data for one reaction repeated three times differed by less than 10% from the average of the three measurements. In summary, reported rate constants are estimated to be within 30% of rate constants that may be determined by more accurate techniques.

Rate constants measured at one temperature were extrapolated to 25, 85, and 120° C by assuming an activation entropy of -28 eu. Activation enthalpies were also calculated.[43] Huisgen made a similar assumption and rate constant extrapolations for the reaction of *C*-phenyl-*N*-methylnitrone with several dipolarophiles.[30]

Some reaction rates were too great at room temperature to measure half-lives by nmr spectroscopy. A lower limit for these rate constants was estimated at 25° and extrapolated to higher temperatures. Rate data are given in Table X.

TABLE X

KINETIC DATA FOR REACTIONS OF N-t-BUTYLNITRONE

Dipolarophile	Solvent	$H^{\ddagger}$ (Kcal)	Rx. Temp.	$k_2 \times 10^5$(l-mole^{-1}-sec^{-1})[a]		
				25°C	85°C	120°C
H-C≡C-CN	CCl_4	≤ 11.5[b]	25°	≥ 2,000[b]	≥ 65,000[b]	≥ 300,000[b]
CH_2=$CHNO_2$	$CDCl_3$	≤ 11.5[b]	25°	≥ 2,000[b]	≥ 65,000[b]	≥ 300,000[b]
CH_2=$CHCO_2CH_3$	CCl_4	≤ 11.5[b]	25°	≥ 2,000[b]	≥ 65,000[b]	≥ 300,000[b]
	$CDCl_3$	≤ 11.5[b]	25°	≥ 2,000[b]	≥ 65,000[b]	≥ 300,000[b]
CH_2=CHC≡N	CCl_4	≤ 11.5[b]	25°	≥ 2,000[b]	≥ 65,000[b]	≥ 300,000[b]
PhN=C=O	CCl_4	12.4	35°	380	15,000	80,000
H-C≡CCO_2Et	CCl_4	12.7	35°	220	9,800	53,000
CH_2=$C(CH_3)CO_2CH_3$	CCl_4	12.9	25°	170	7,800	43,000
CH_2=C(OAc)CN	CCl_4	12.9	25°	150	7,100	39,000
CH_2=$C(CH_3)$CN	CCl_4	13.2	25°	110	5,300	30,000
CH_2=$CHSO_2$Ph[c]	$CDCl_3$	13.4	35°	73	3,900	23,000
CH_3CH=CHCHO	CCl_4	15.0	70°	5.1	420	3,000
CH_2=CHPh	CCl_4	15.3	70°	2.8	260	1,900
CH_2=CHSPh	CCl_4	15.4	80°	2.2	210	1,600
CH_2=$CHOCH_2CH(CH_3)_2$	CCl_4	15.5	80°	2.1	200	1,500
	CCl_4	15.8	70°	1.2	130	1,000

Continued

Table X

$H-C{\equiv}CPh$[d]	CCl_4	15.8	70°	1.1	120	970
$CH_3CH{=}CHCO_2CH_3$	CCl_4	16.3	80°	0.51	61	520
$CH_2{=}CH{-}OC(=O)CH_3$	CCl_4	16.3	80°	0.49	60	510
$PhCH{=}CHCO_2CH_3$	CCl_4	16.6	80°	0.33	43	370
$PhCH{=}CHCHO$	CCl_4	16.7	80°	0.28	38	330
$CH_2{=}CH(CH_2)_2Ph$	CCl_4	16.7	80°	0.27	37	320
$CH_2{=}C(CH_3)Ph$	CCl_4	17.0	80°	0.17	25	230
$H-C{\equiv}C-(CH_2)_3Ph$	CCl_4	17.5	90°	0.067	11	110
$CH_3CH{=}CHPh$	CCl_4	19.1	120°	0.0044[e]	1.2[e]	14[e]

a. Refer to Sections II B and III C for an estimate of errors and for experimental details for these data. All disubstituted alkenes are the trans isomers.

b. These reactions were exothermic and half-lives were too short at 25° to be measured by nmr spectroscopy.

c. Rate constants were extrapolated from the average of two rate constants measured by nmr spectroscopy. One rate constant was determined by peak height measurements and the other by integrated area measurements. The two rate constants differed by less than 5% from the average of the two values.

d. Rate constants are the average of three extrapolations from three different rate constants measured by nmr spectroscopy. The original data were determined by peak height measurements and each of the three rate constants differed by less than 5% from the average of the three values.

e. N-t-Butylnitrone decomposed rapidly at 120° and these rate constants are only approximate.

The crossover in the control of reactivity of N-t-butylnitrone cycloadditions is shown in Figure 14 with three examples from Table X. The HO energies of N-t-butylnitrone and the dipolarophiles are taken as the negative of their ionization potentials and the LU energies are estimated from experimental data and/or calculations (Section II A). A graph of the ionization potentials of the dipolarophiles versus the rate constants of Table X has generally a U shape.

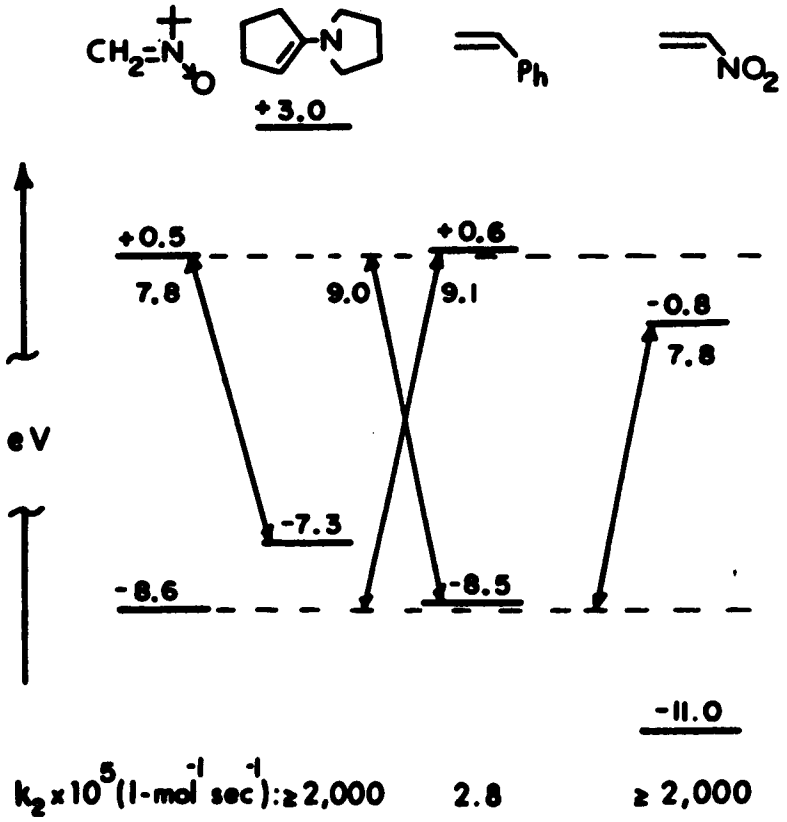


Figure 14. Crossover in the Control of Reactivity of N-t-Butylnitrone Cycloadditions

Since steric effects are not taken into account in the frontier orbital treatment of these reactions, rate constants for reaction of two alkenes which have similar ionization potentials can be quite different if steric effects are much different for the two reactions. Styrene (I.P. = 8.48 eV)[10] for example, is 600 times more reactive with N-t-butylnitrone

than trans-β-methylstyrene (I.P. = 8.38 eV)[26a] at 25°. Isopropenyl acetate (I.P. = 9.74 eV)[26a] is totally unreactive with N-t-butylnitrone, even at 120°, whereas vinyl acetate (I.P. = 9.85 eV)[26a] and N-t-butylnitrone react slowly at 80°. Steric effects in the reactions of C-phenyl-N-methylnitrone with alkenes was reviewed in Section I C. Additional discussion on steric effects is given below.

A subtle verification of frontier orbital rationalizations of reactivity is provided by the reactions of C-phenyl-N-methylnitrone with p-substituted styrenes. The reaction of C-phenyl-N-methylnitrone (I.P. = 7.89 eV)[26a] and styrene (I.P. = 8.48 eV)[10] is dipole HO controlled. Electron-releasing substituents on styrene will raise the energies of the HO and LU orbitals, causing a decrease in the dominant frontier orbital interaction and a decrease in the rate of the reaction. Electron-withdrawing substituents on styrene will lower the energies of both the HO and LU orbitals and increase the reaction rate relative to that of styrene. The data of Huisgen[30] are summarized in Table XI.

TABLE XI

Reactions of C-Phenyl-N-Methylnitrone with p-Substituted Styrenes

Dipolarophile	$10^5 k_2$ (l-mole^{-1}sec^{-1}) (Toluene, 120°)
p-Nitrostyrene	51.0
p-Chlorostyrene	19.7
Styrene	11.7
p-Methylstyrene	9.3
p-Methoxystyrene	8.72

The reaction constant, ρ, for this set of reactions is positive which, in a classical treatment of this type of data, suggests that the transition states for these cycloadditions have a charge distribution which is stabilized by electron-withdrawing substituents and destabilized by electron-donating substituents on styrene. Polar transition states or dipolar intermediates in these reactions should be reflected by greater reaction rates in more polar solvents. In fact Huisgen[30] has found that cycloadditions of C-phenyl-N-methylnitrone are slower by a factor of five to six in more polar solvents (Section I C). Similar results have been obtained in these studies and are discussed below. The frontier orbital interpretation of these data is more satisfactory.

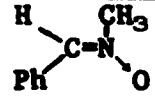
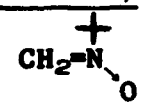
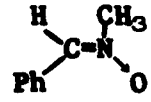
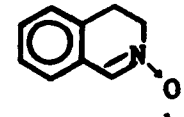
The relative reactivities of different nitrones can also be rationalized by frontier orbital concepts. Substituents in conjugation with the 4 π electron system of nitrones compress the frontier orbital energies (Section II A). The HO orbital and the LU orbital of C,N-diphenylnitrone, for example, are higher and lower, respectively, in energy than the corresponding frontier orbitals of C-phenyl-N-methylnitrone. Consequently, the frontier orbital interactions of C,N-diphenylnitrone with a given dipolarophile are always greater than the corresponding interactions of C-phenyl-N-methylnitrone and the former should be the more reactive nitrone. In accord with these ideas, the rate constants for the reaction of C-phenyl-N-methylnitrone, C,N-diphenylnitrone, and C-benzoyl-N-phenylnitrone with ethyl crotonate in toluene at 100° are 10.7, 55.0, and 6200, respectively.[30]

The HO orbital and the LU orbital energies of C-phenyl-N-methylnitrone are higher and lower, respectively, than the corresponding

frontier orbital energies of N-t-butylnitrone (Figure 13). Consequently, considering electronic factors only, C-phenyl-N-methylnitrone should be more reactive than N-t-butylnitrone with any given dipolarophile. However, just the opposite is observed. Rate data illustrating these observations are given in Table XII.

TABLE XII

A COMPARISON OF THE REACTION RATES OF C-PHENYL-N-METHYLNITRONE, N-t-BUTYLNITRONE, AND 3,4- DIHYDROISOQUINOLINE N-OXIDE[a]

Dipolarophile	Rate I $10^5 k_2$(l-mole^{-1}-sec^{-1}) 	Rate II $10^5 k_2$(l-mole^{-1}-sec^{-1}) 	Ratio II/I
Methyl acrylate	384[b]	≥ 300,000[c]	≥ 781
Acrylonitrile	279[b]	≥ 300,000[c]	≥ 1075
Phenyl isocyanate	1710[b]	80,000[c]	47
Methyl methacrylate	129[b]	43,000[c]	333
Ethyl crotonate	32.5[b]		
Methyl crotonate		520[c]	16
Styrene	11.7[b]	1,900[c]	162
Allyl acetate	7.25[b]		
Vinyl acetate		510[c]	70
1-Heptene	2.64[b]		
4-Phenyl-1-butene		320[c]	121
α-Methylstyrene	1.07[b]	230[c]	215
Cyanoacetylene	5500[d]	≥ 300,000[c]	≥ 55
			
Ethyl Crotonate	2400[b]	10.7[b]	224

a. All rates were either measured at 120° or extrapolated to 120° assuming an entropy of activation of -28 eu.

b. Ref. 30. Toluene was used as the solvent.

c. This work (see discussion, page 72). Carbon tetrachloride was used as the solvent.

d. This work (see discussion, page 72). Deuterochloroform was used as the solvent.

The sterically unencumbered N-t-butylnitrone should be more reactive than the sterically hindered C-phenyl-N-methylnitrone. However, the large difference in the reactivity of C-phenyl-N-methylnitrone and N-t-butylnitrone with the very reactive dipolarophiles, methyl acrylate and acrylonitrile, cannot be attributed solely to steric factors. Apparently, electronic factors which are not clearly identifiable in the qualitative ideas of frontier orbital theory account for these inordinately large rate differences.

Other data of Table XII show that N-t-butylnitrone is from 16 to 333 times more reactive with a given dipolarophile than C-phenyl-N-methylnitrone. These differences may be attributed largely to steric factors. Supporting this conclusion is the fact that 3,4-dihydroisoquinoline N-oxide is 224 times more reactive with ethyl crotonate than the electronically similar but sterically different C-phenyl-N-methylnitrone.

2. Regioselectivity in Nitrone Cycloadditions

The regioselectivity of nitrone cycloadditions can be rationalized also by frontier orbital concepts. The preferred regioisomer in nitrone cycloadditions will be that one in which the larger terminal coefficients of the interacting frontier orbitals are united (Section II A). The frontier orbital interactions may be LU controlled, LU, HO controlled, or HO controlled. The free radical theory of Firestone[7] and the steric arguments of Huisgen[9] discussed in Section I C do not account for the products formed in reactions of nitrones with very electron-deficient dipolarophiles, and these arguments are no longer necessary to account for the products formed in other nitrone cycloadditions.

a. Reactions with Electron-rich Dipolarophiles

The frontier orbital interactions of N-t-butylnitrone with electron-rich dipolarophiles are shown in Figure 15. The terminal coefficients of the HO orbital of N-t-butylnitrone are approximately the same and the larger terminal coefficient of the LU orbital is on carbon. Electron-rich dipolarophiles have the largest terminal coefficient on the carbon removed from the substituent in the HO orbital and on the carbon attached to the substituent in the LU orbital (Section II A). The reactions of electron-rich dipolarophiles with the sterically unencumbered N-t-butylnitrone are LU controlled and all cycloadducts isolated are 5-substituted isoxazolidines, 5-substituted isoxazolines, or compounds derived from these products. Steric arguments are unnecessary in explaining these results. Reaction yields and reaction rates are summarized in Table XIII.

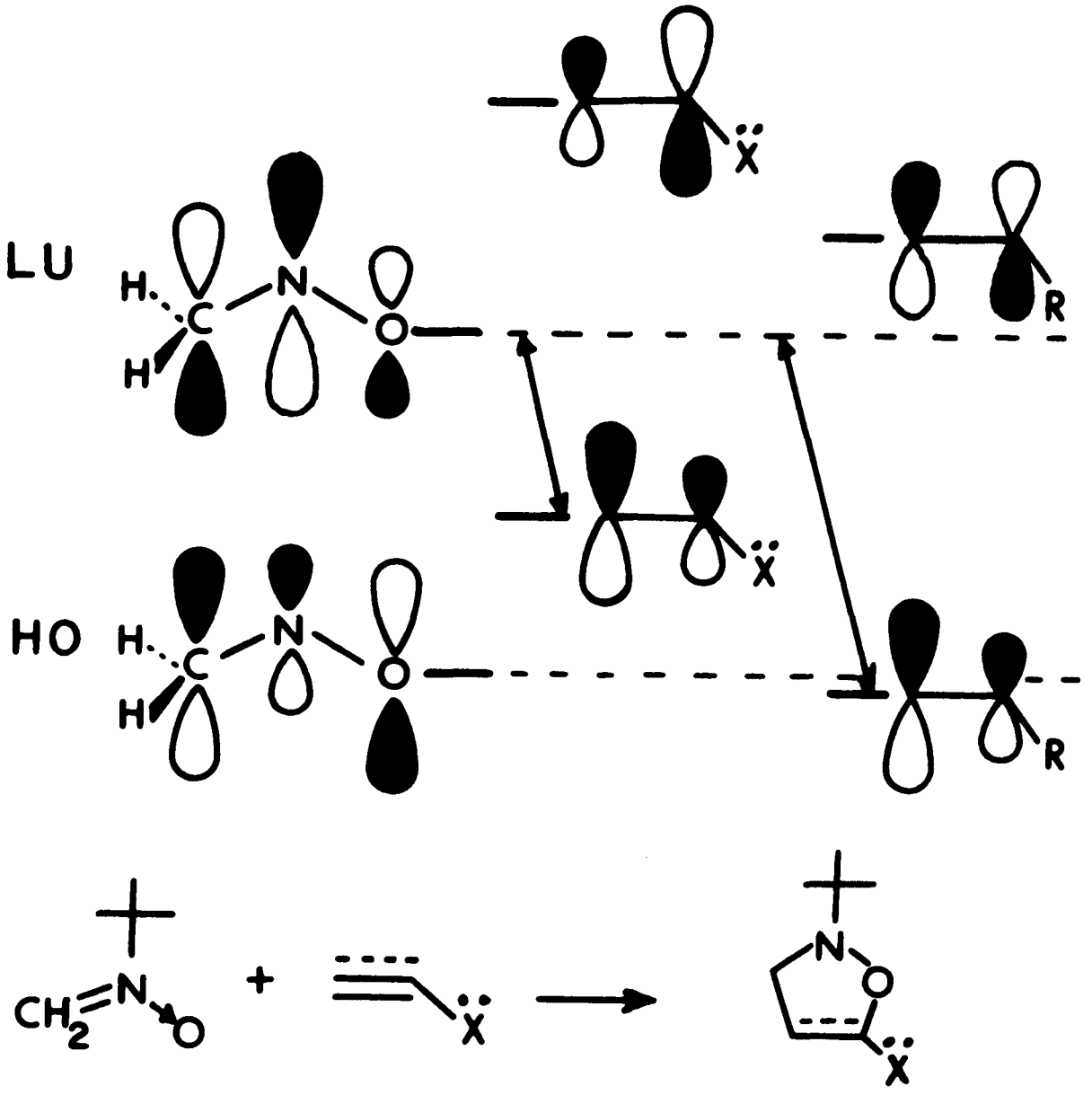


Figure 15. Frontier Orbital Interactions of N-t-Butylnitrone with Electron-Rich Dipolarophiles

TABLE XIII

REACTIONS OF N-t-BUTYLNITRONE WITH ELECTRON-RICH DIPOLAROPHILES

Dipolarophile	Product	%Yield	Rate Constant(25°)[a] $10^5 k_2$(l-mole^{-1}sec^{-1})
1-(N-Pyrrolidino)-1-cyclopentene	A		≥ 2,000
Phenyl vinyl sulfide	C	96	2.2
Isobutyl vinyl ether	C	61	2.1
1-(N-Morpholino)-1-cyclohexene	B[b]		1.2
Vinyl acetate	C	46	0.49
4-Phenyl-1-butene	C	87	0.27
5-Phenyl-1-pentyne	D	36	0.067
Ethoxyacetylene	E		
Isopropenyl acetate	E		

a. See Table X.

b. Nmr and ir spectra shown in Appendices A and B.

A, Product(s) not isolated. Only the reaction rate was measured; B, structure of isolated product not determined; C, 5-substituted isoxazolidine; D, isolated as 1-t-butyl-2-(4-phenylbutyryl)-aziridine; E, No reaction. See Section III C for experimental details.

Structure Proofs

The structures of the 5-substituted isoxazolidines were immediately apparent from their nmr spectra. The absorption for the C-5 ring proton of each product appeared as a multiplet in the range δ 6.30-3.55. The absorptions for the C-3 and C-4 ring protons appeared as multiplets in the range 3.20-1.50 ppm. Nmr spectra of typical 4- and 5-substituted isoxazolidines and 4- and 5-substituted isoxazolines are shown in Appendix A. Spectral data and elemental analysis for new compounds are given in Section III C.

The anticipated 5-morpholinoisoxazolidine was not isolated from the reaction of N-t-butylnitrone and 1-(N-morpholino)-1-cyclohexene.

Several preparations always gave a white crystalline compound (40) of mp 108-111°. Elemental analysis and mass spectral data indicated that the empirical formula of the substance is $C_{11}H_{21}NO_2$, which is consistent with the loss of morpholine and addition of water to a 1:1 adduct. No structure assignment was made for this compound. The formation of unusual and frequently unidentifiable products in the reactions of enamines and nitrones has been described in the literature and has been reviewed in Section I C.

The only product isolated from the reaction of N-t-butylnitrone and 5-phenyl-1-pentyne was 1-t-butyl-2-(4-phenylbutyryl)-aziridine, presumably formed by the rearrangement of 2-t-butyl-5-(3-phenylpropyl)-Δ^4-isoxazoline. Spectral data (a carbonyl absorption in the ir spectrum and no olefinic protons in the nmr spectrum) and elemental analysis confirm the structure of the aziridine. Rearrangements of isoxazolines are discussed later in this Section.

b. Reactions with Conjugated Dipolarophiles

The frontier orbital interactions of N-t-butylnitrone and conjugated dipolarophiles are shown in Figure 16. Both frontier orbital interactions are appreciable for most conjugated dipolarophiles and the reactions are LU, HO controlled. Since the HO coefficients of N-t-butylnitrone are approximately equal, regioselectivity is still controlled by the nitrone LU orbital coefficients and only the 5-substituted isoxazolidines and 5-substituted isoxazolines are formed. Steric arguments are unnecessary to explain these results. Reaction yields and reaction rates are summarized in Table XIV.

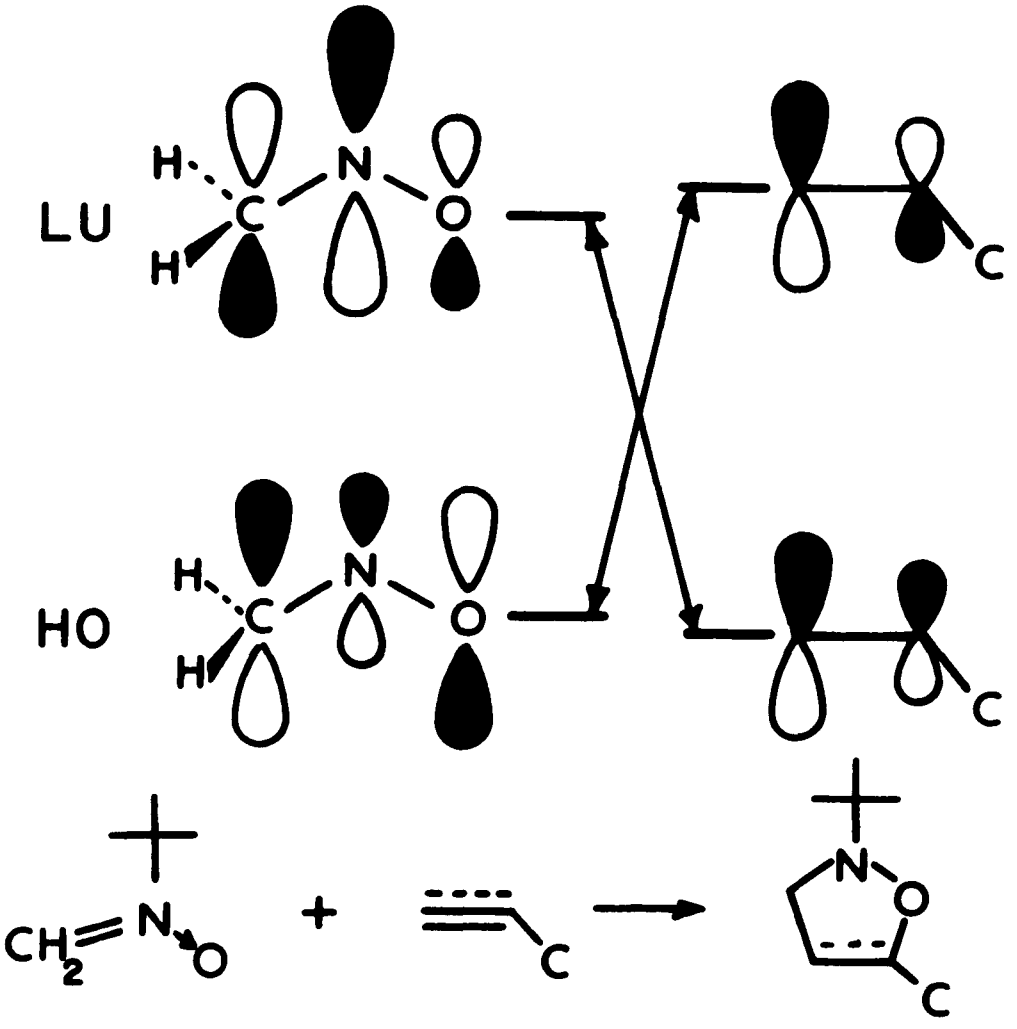


Figure 16. Frontier Orbital Interactions of N-t-Butylnitrone with Conjugated Dipolarophiles

TABLE XIV

REACTIONS OF N-t-BUTYLNITRONE WITH CONJUGATED DIPOLAROPHILES

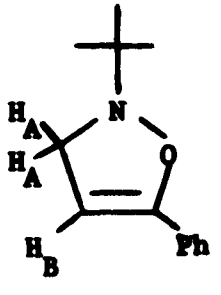
Dipolarophile	Product	%Yield	Rate Constant $(25^{\circ})^{a}$ $10^{5}k_{2}$(l-mole^{-1}-sec^{-1})
Styrene	A	73	2.8
Phenylacetylene	B	80	1.2
α-Methylstyrene	A	72	0.17
trans-β-Methylstyrene	A	46	0.0044

a. See Table X.
A, 5-substituted isoxazolidine; B, 5-substituted isoxazoline.

Structure Proofs

The chemical shifts and splitting patterns in the nmr spectra of the styrene adducts were characteristic of 5-substituted isoxazolidines. The chemical shifts of the C-5 proton of the styrene and trans-β-methylstyrene adducts are δ 4.86 dd and δ 4.28 d, respectively. The resonances due to the C-3 and C-4 methylene protons of the α-methylstyrene adduct are centered at 2.50 ppm.

The structure of the phenylacetylene adduct, 2-t-butyl-5-phenyl-Δ^{4}-isoxazoline (41), was not immediately obvious from its nmr spectrum since only one of the two possible regioisomers was formed.



δ_{A} 4.00 d

δ_{B} 5.00 t

J_{AB} = 2.5 Hz

41

However, both 4- and 5-substituted isoxazolines were isolated and characterized in reactions described below and the phenylacetylene adduct can definitely be assigned the structure 41 by a comparison of its nmr spectrum to those of other isoxazolines.

c. Reactions with Electron-deficient Dipolarophiles

The frontier orbital interactions of N-t-butylnitrone and electron-deficient dipolarophiles are shown in Figure 17. The dominant frontier orbital interaction is between dipole HO and dipolarophile LU, and the reactions are HO controlled. Since the HO coefficients of N-t-butylnitrone are approximately equal, regioselectivity is still controlled by the nitrone LU orbital coefficients. Only the 5-substituted isoxazolidines are formed from the monosubstituted and the 1,1-disubstituted alkenes for which the larger coefficient in the HO orbital is always on the carbon removed from the substituents. The 1,2-disubstituted alkenes have HO and LU orbital coefficients which are more nearly equal (Section II A); consequently, regioselectivity is lost and a mixture of both 4- and 5-substituted isoxazolidines are formed. Again, steric arguments are unnecessary to explain these results. Reaction yields and reaction rates are summarized in Table XV.

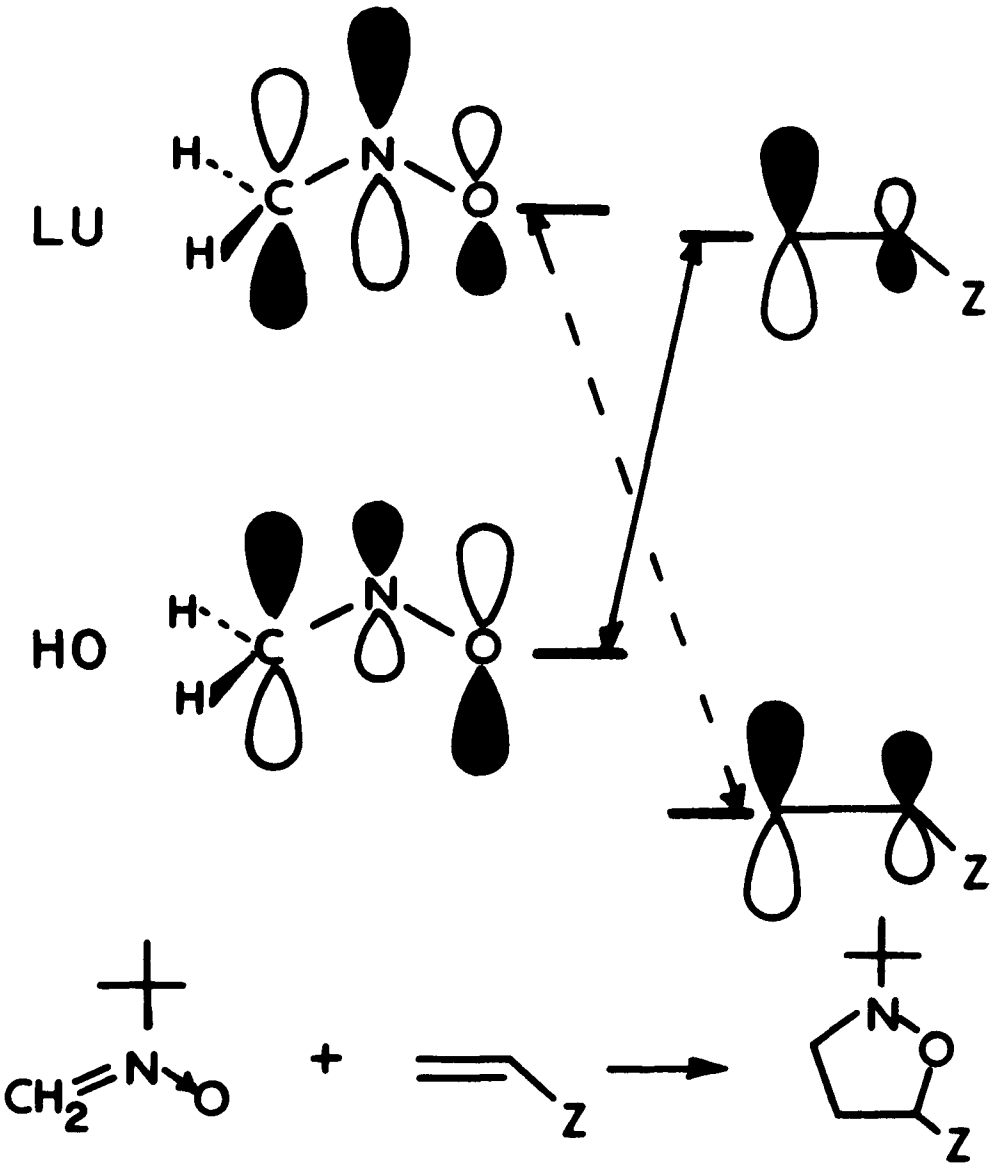


Figure 17. Frontier Orbital Interactions of N-t-Butylnitrone with Electron-Deficient Dipolarophiles

TABLE XV

REACTIONS OF N-t-BUTYLNITRONE WITH ELECTRON-DEFICIENT DIPOLAROPHILES

Dipolarophile	Product	Yield%	Rate Constant (25°)[a] $10^5 k_2$(l-mole^{-1}-sec^{-1})
Methyl acrylate	A[b]	78	≥ 2,000
Acrylonitrile	A	72	≥ 2,000
Methyl methacrylate	A	58	170
1-Acetoxyacrylonitrile	A	79	150
α-Methylacrylonitrile	A	72	110
Crotonaldehyde		49	5.1
	A	53	
	B	47	
Methyl crotonate		67	0.51
	A[c]	40	
	B[d]	60	
Methyl cinnamate		89	0.33
	A[b]	31	
	B[b]	69	
Cinnamaldehyde	C		0.28
Vinylidene cyanide	D		

a. See Table X.

b. See nmr spectrum in Appendix A.

c. See nmr spectrum in Figure 18.

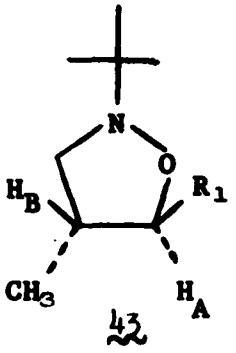
d. See nmr spectrum in Figure 19.

A, 5-substituted isoxazolidine; B, 4-substituted isoxazolidine; C, products not isolated. Only the reaction rate was measured. D, no reaction. See Section III C for experimental details.

Structure Proofs

The nmr spectra of the 5-substituted cycloadducts of methyl acrylate (42), methyl methacrylate, acrylonitrile, and substituted acrylonitriles were all very similar. The absorptions of the C-3 and C-4 ring protons of these adducts were multiplets with chemical shifts in the range δ 3.20-1.50

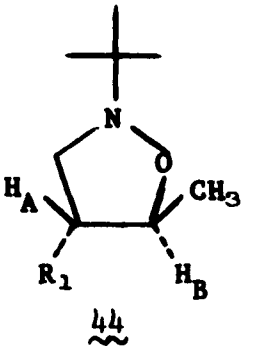
with complex splitting patterns characteristic of adjacent methylene groups. The C-5 proton absorptions of the methyl acrylate and acrylonitrile adducts were centered at 4.30 and 4.60 ppm, respectively, and are characteristic chemical shifts of 5-substituted isoxazolines.



43

a R_1 = CHO

b R_1 = CO_2CH_3



44

The crotonaldehyde adducts 43a and 44a were isolated in a ratio of 53:47. The nmr spectra of these compounds clearly reveal their identities. The C-5 proton (H_A) absorption of 43a is a doublet of doublets centered at δ 3.56 and coupled to H_B (J = 4.0 Hz) and to the aldehydic proton (J = 1.5 Hz). The C-5 proton absorption (H_B) of 44a appears as a five-line pattern centered at δ 4.10. The remaining three ring protons appear as a complex multiplet at 3.35-1.85 ppm.

The methyl crotonate adducts 43b and 44b were isolated in the ratio of 40:60. The chemical shifts of the ring protons of 43b and 44b were very similar and definite structure assignments were made only after spin decoupling experiments were completed. The spin decoupled spectra of the two regioisomers are shown in Figures 18 and 19.

A 31:69 mixture of methyl cinnamate adducts 45 and 46 could not be separated by preparative layer chromatography. However, the ratio of regioisomers was determined by integration of the proton absorptions of H_A and H_B which were well resolved in the nmr spectrum of

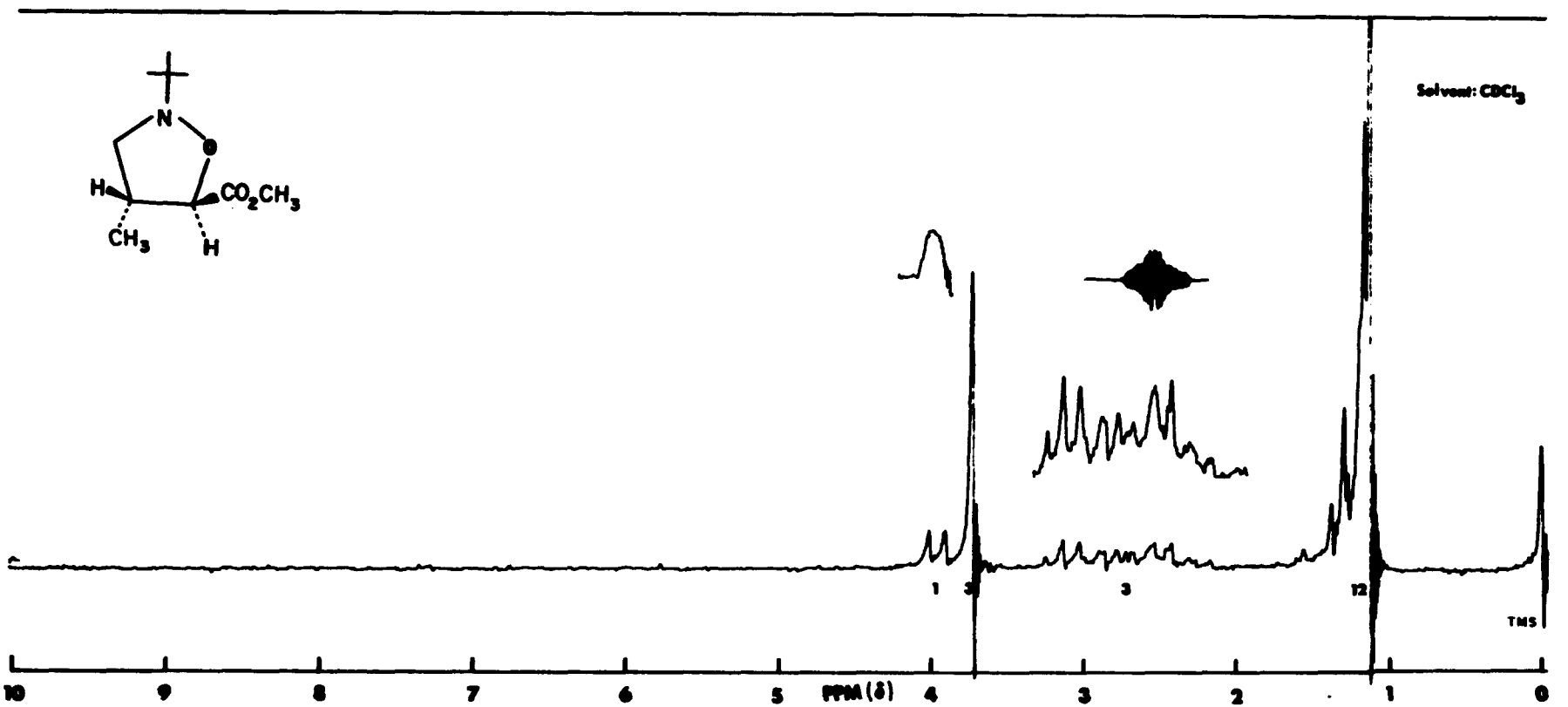


Figure 18. Nmr Spectrum of <u>trans</u>-2-<u>t</u>-Butyl-4-Methyl-5-Carbomethoxyisoxazolidine

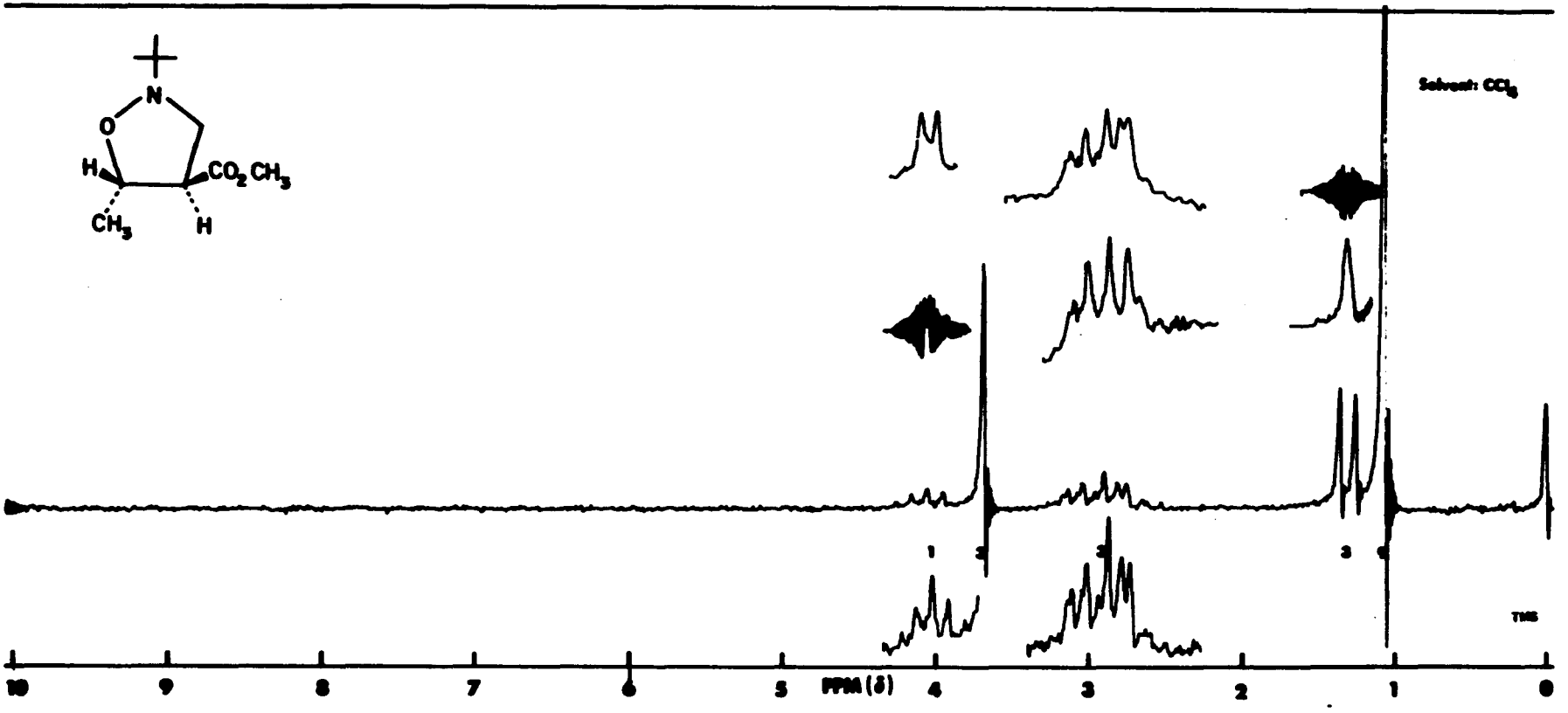
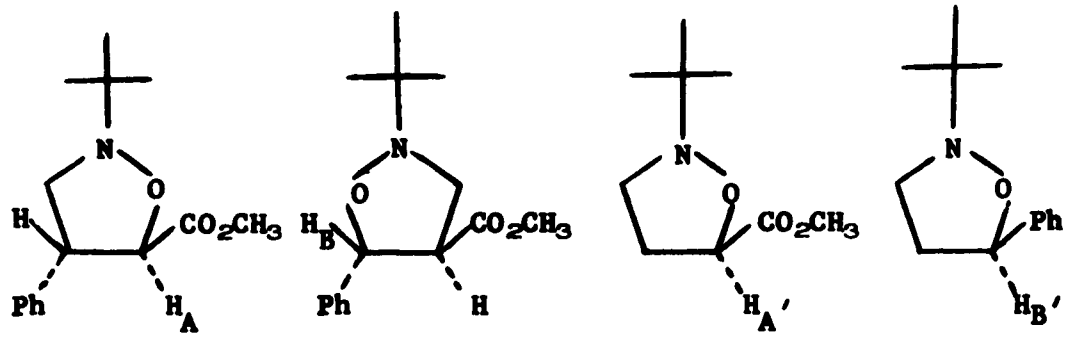


Figure 19. Nmr Spectrum of <u>trans</u>-2-<u>t</u>-Butyl-4-Carbomethoxy-5-Methylisoxazolidine



45 46 47 48

the mixture. Proton H_A was assigned to an absorption at δ 4.26 d, and proton H_B was assigned to an absorption at δ 5.00-5.30 m. Consistent with these assignments are the chemical shifts of proton H_A' [δ 4.30 dd] of 47 and H_B' [δ 4.86 dd] of 48. The remaining ring protons of 45 and 46 appear as a broad multiplet centered at 3.15 ppm.

d. Reactions with Very Electron-deficient Dipolarophiles

The frontier orbital interactions of nitrones (N-t-butylnitrone and C-phenyl-N-methylnitrone) and very electron-deficient dipolarophiles are shown in Figure 20. Very strong electron withdrawing groups lower the frontier orbital energies (HO and LU) of these dipolarophiles so that the reactions are strongly HO controlled. The HO orbital energy of ethyl propiolate (I.P. = 11.15 eV),[10] for example, is lower than the HO orbital energy of methyl acrylate (I.P. = 10.72 eV),[10] and the interaction of the dipole HO orbital with the dipolarophile LU orbital (which favors formation of the 4-substituted adduct) is greater with the propiolate than with the acrylate. The same comparison can be made between cyanoacetylene (I.P. = 11.81 eV)[10] and acrylonitrile (I.P. = 10.91 eV).[10]

Regioselectivity in these cycloadditions is controlled by the terminal coefficients of the dipole HO and dipolarophile LU orbitals, and the formation of 4-substituted isoxazolidines and 4-substituted isoxazolines was predicted. These ideas were confirmed and reaction data are given in Table XVI.

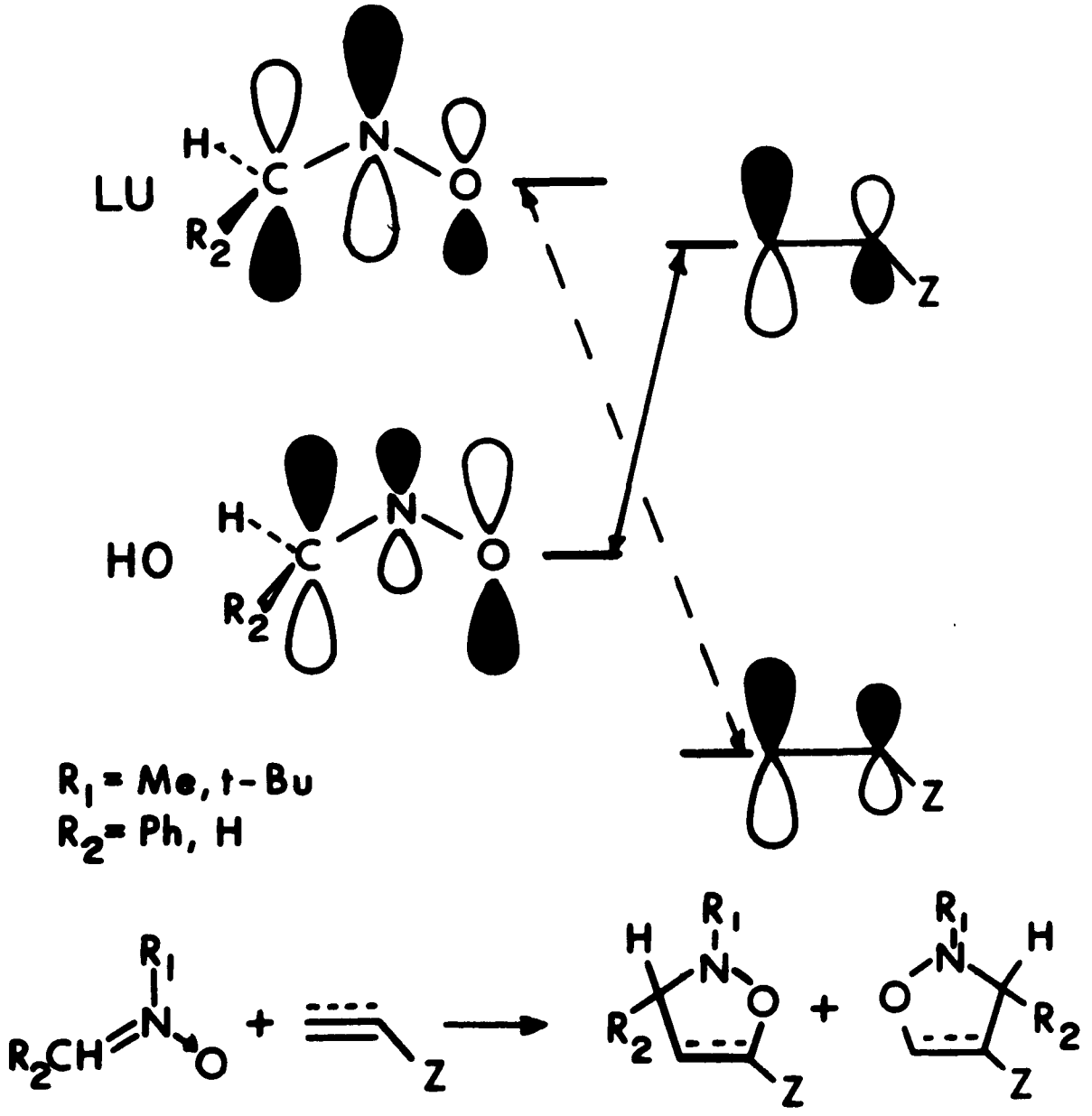


Figure 20. Frontier Orbital Interactions of C-Phenyl-N-Methylnitrone and N-t-Butylnitrone with Very Electron-Deficient Dipolarophiles

TABLE XVI

REACTIONS OF N-t-BUTYLNITRONE AND C-PHENYL-N-METHYLNITRONE WITH VERY ELECTRON-DEFICIENT DIPOLAROPHILES

Dipolarophile	Ratio of Products A:B	Yield%	Rate Constant (25°)[a] $10^5 k_2$(l-mole^{-1}-sec^{-1})
	N-t-Butylnitrone		
Cyanoacetylene	50:50[b]	58	≥ 2,000
Nitroethylene	100:0	c	≥ 2,000
Ethyl propiolate	70:30	71	220
Phenyl vinyl sulfone	70:30[b]	98	73
	C-Phenyl-N-Methylnitrone		
Cyanoacetylene	0:100	82	14
Nitroethylene	0:100	76	7.5
Ethyl propiolate	42:58[d]	92[d]	d
Phenyl vinyl sulfone	32:68[b]	86	0.20

a. See Table X and Table XVII.

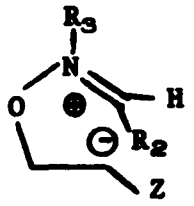
b. See nmr spectrum in Appendix A.

c. Product not isolated. See Section III C for experimental details.

d. Reported by Huisgen, Chem. Ber., 102, 904 (1969), and rate data were not given.

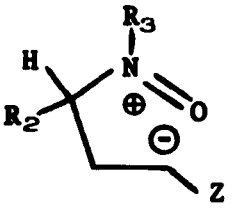
A, 5-substituted isoxazolidine or 5-substituted isoxazoline; B, 4-substituted isoxazolidine or 4-substituted isoxazoline.

The loss of regioselectivity in the reactions of nitrones with very electron-deficient dipolarophiles might at first glance be construed as evidence for the formation of dipolar intermediates in these cycloadditions. The 4-substituted (reversed) products are those isomers expected to be favored in the reactions of C-phenyl-N-methylnitrone if dipolar intermediates are formed. That is, the zwitterion 49a is expected to be more stable than the zwitterion 50a. Similarly, 49b



a R_2 = Ph, R_3 = CH_3

b R_2 = H, R_3 = t-butyl



49 50

should be more stable than 50b. Dipolar intermediates formed from very electron-deficient dipolarophiles, i.e., when Z = NO_2, SO_2Ph, or C≡N, should be especially stable. Formation of these zwitterions should be facilitated by highly polar solvents, and cycloadditions involving an increase in charge separation should exhibit a strong enhancement of rate with increasing solvent polarity. On the other hand, a concerted reaction would show little or no change in rate with a change in solvent polarity.

To test whether reactions of very electron-deficient dipolarophiles involve dipolar intermediates, rate constants for a representative reaction of this type were measured in four different solvents. The reaction of C-phenyl-N-methylnitrone and cyanoacetylene shows reversed regioselectivity and was an ideal choice for these studies. Rate data are summarized in Table XVII. The rate acceleration by an increase in solvent polarity expected if dipolar intermediates were formed was not observed. In fact, the reaction rate was slower in methanol-d_4 than in benzene-d_6. Similar results obtained by Huisgen[30] were discussed in Section I C.

The dipole moments of the very electron-deficient dipolarophiles could conceivably influence regiochemistry in nitrone cycloaddition

TABLE XVII

KINETIC DATA FOR C-PHENYL-N-METHYLNITRONE REACTIONS

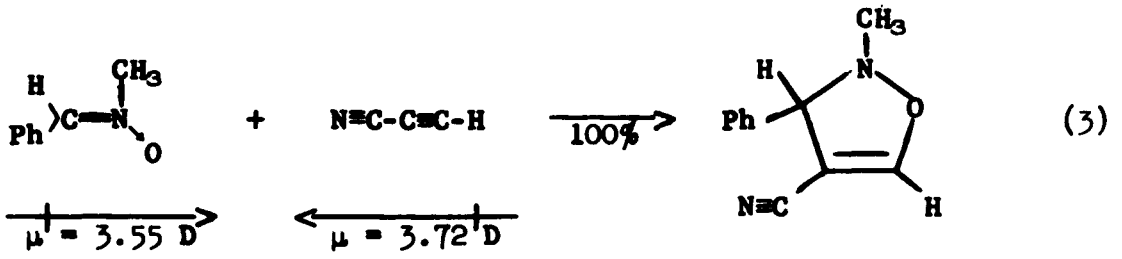
Peak Height	Integrated Height	Solvent	$H^{\ddagger}$, kcal	$k_2 \times 10^5$ (l-mole^{-1}-sec^{-1})[a] 25° C	85° C	120° C
		Reactions of C-Phenyl-N-Methylnitrone with Cyanoacetylene at 35°[b]				
X		C_6D_6	14.2	19	1,300	8,200
	X	C_6D_6	14.2	19	1,200	8,000
X	(D-C≡C-C≡N)[c]	$CDCl_3$	14.3	15	1,000	6,800
X		DMSO-d_6	14.3	15	1,000	6,700
X		$CDCl_3$	14.4	14	980	6,500
	X	$CDCl_3$	14.4	13	900	6,000
X	(D-C≡C-C≡N)	D_3COD	15.2	3.4	300	2,200
		Reaction of C-Phenyl-N-Methylnitrone with Nitroethylene at 60°				
X		$CDCl_3$	14.7	7.5	580	4,000
		Reaction of C-Phenyl-N-Methylnitrone and Phenyl Vinyl Sulfone at 80°				
X		$CDCl_3$	16.9	0.20	28	260

a. Rate constants were measured by nmr spectroscopy. Refer to Sections II B and III C for an estimate of errors and for experimental details for these data.

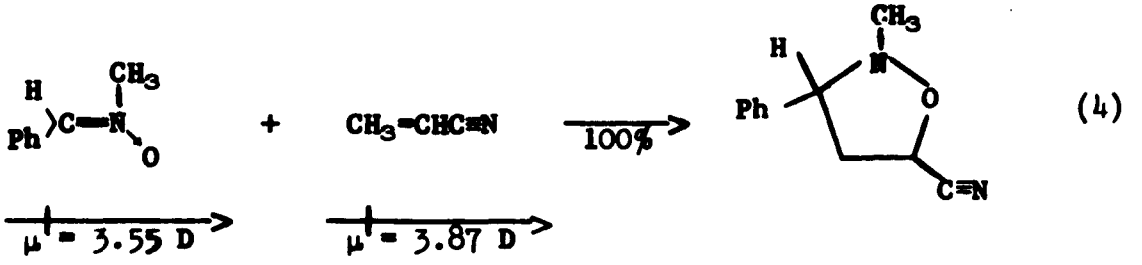
b. Reactions were followed without interruption by nmr spectroscopy and reported rates are estimated to be within 10% of values that may be determined by more accurate techniques.

c. Cyanoacetylene is instantly deuterated in D_3COD.

reactions. In a concerted cycloaddition, the reactants approach each other in parallel planes with no solvent molecules between them in the transition state (Section I C). Electrostatic forces influence the approach of the two molecules until the distance separating them is small enough for covalent bonding to begin. The most favorable electrostatic interaction of the approaching reactants is that in which their dipole moments are antiparallel. It appears as though the reversal of regioselectivity in the reaction of C-phenyl-N-methylnitrone (μ = 3.55 D)[30] and cyanoacetylene (μ = 3.72 D)[44] shown in equation (3)[a] could be controlled by the dipole moments of the reactants.



(3)



(4)

However, the reaction of C-phenyl-N-methylnitrone with acrylonitrile (μ = 3.87 D)[44] shown in equation (4)[b] gives only the most "electrostatically unfavorable" product. The regiochemistry observed in both of these reactions is in accord with frontier orbital theory. The dipole

---

a. This work.

b. Reference 45.

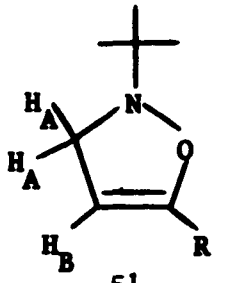
LU - dipolarophile HO interaction strongly favors formation of the 5-substituted adduct of Equation (4), whereas the dipole HO - dipolarophile LU interaction only weakly favors formation of the 4-substituted adduct of Equation (3) because of the similar coefficients of the HO orbital. Not until the latter interaction becomes much greater than the former does reversal of regiochemistry occur. Once the dipole LU interaction is sufficiently small, dipole-dipole interactions which favor formation of the 4-substituted product of Equation (3) may become dominant.

The data of Table XVI are consistent with other qualitative predictions of frontier orbital theory. Cyanoacetylene (I.P. = 11.81 eV);[10] for example, has lower frontier orbital energies (greater frontier orbital interactions with the nitrone HO) than those of ethyl propiolate (I.P. = 11.15 eV)[10] consequently, in accord with theory, cyanoacetylene shows greater reactivity and greater formation of the reversed regioisomer with a given nitrone. The HO orbital energy of C-phenyl-N-methylnitrone (I.P. = 7.89 eV) is higher than the HO orbital energy of N-t-butylnitrone (I.P. = 8.64 eV) and, in accord with theory, C-phenyl-N-methylnitrone has a greater propensity (greater HO frontier orbital interaction) than N-t-butylnitrone for formation of the reversed regioisomers with very electron-deficient dipolarophiles. In addition, these data show that regioselectivity is controlled by electronic and not steric factors. N-t-Butylnitrone reacts with cyanoacetylene and ethyl propiolate to give a mixture of regioisomers while the same nitrone reacts with the sterically similar acrylonitrile and methylacrylate to give only the normal adducts. More convincingly, C-phenyl-N-methylnitrone reacts regioselectively with cyanoacetylene and

nitroethylene to give the more sterically hindered 4-substituted heterocycles.

Structure Proofs

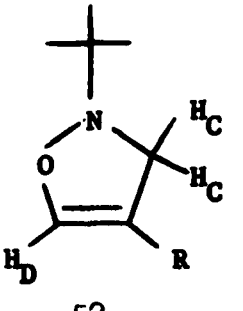
Cyanoacetylene and N-t-butylnitrone reacted rapidly and exothermically at 25° in CCl_4 to give a 50:50 mixture of isoxazolines 51a and 52a.



51

a R = C≡N

b R = $CO_2C_2H_5$



52

Structure assignments from spectral data were especially straightforward since both regioisomers were isolated. The ring protons of both isomers have a characteristic AX_2 spin-spin coupling pattern in their nmr spectra. The chemical shifts for the olefinic protons H_B of the normal isomer 51a and H_D of the reversed isomer 52a are δ 5.62 t and δ 7.10 t, respectively. The chemical shifts of the methylene protons H_A of the normal isomer and H_C of the reversed isomer are both δ 4.05 d. Coupling constants for 51a and 52a are J_{AB} = 3.0 Hz and J_{CD} = 2.0 Hz, respectively. The large difference in the chemical shifts of the olefinic protons in the two regioisomers makes these structural assignments unambiguous.

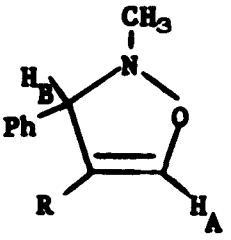
Ethyl propiolate and N-t-butylnitrone reacted rapidly and exothermically at 25° in CCl_4 to give a 70:30 mixture of 51b and 52b. Coupling constants and chemical shifts for the ring protons of these regioisomers were essentially identical to those of the cyanoacetylene

adducts: δ_A 4.00 d, δ_B 5.60 t, J_{AB} = 2.5 Hz; and δ_C 4.00 d, δ_D 7.11 t, J_{CD} = 2.0 Hz.

Nitroethylene and N-t-butylnitrone reacted rapidly and exothermically at 25° in CCl_4 to give only 2-t-butyl-5-nitroisoxazolidine. The product was stable indefinitely in the reaction solvent under nitrogen, but decomposed rapidly on either silica gel or aluminum oxide plc plates. The nmr spectrum (CCl_4) is characteristic of 5-substituted isoxazolidines: δ 2.60-3.20 ($-CH_2CH_2-$, m, 4H) and 5.40-5.60 ($OCHNO_2$, m, 1H).

Phenyl vinyl sulfone and N-t-butylnitrone reacted quantitatively at 50° to give a 70:30 mixture of the normal and reversed regioisomers which could not be separated by plc. The ratio of isomers was determined by nmr spectroscopy. The normal adduct, 2-t-butyl-5-benzenesulfonylisoxazolidine (53), was isolated as a solid (mp = 91-93°) by fractional crystallization from the reaction mixture. The ring protons in the nmr spectrum of 53 in $CDCl_3$ were characteristic of 5-substituted isoxazolidines: δ 2.40-3.20 ($-CH_2CH_2-$, m, 4H) and δ 4.70-5.10 ($CHSO_2Ph$, m, 1H). The reversed regioisomer, 2-t-butyl-4-benzenesulfonylisoxazolidine (54), was obtained in 67% purity by fractional crystallization of 53. The C-4 and C-5 ring protons ($-OCH_2CHSO_2Ph$) appeared as a broad multiplet at δ 3.80-4.40 and the C-3 methylene protons appeared as a multiplet at δ 3.00-3.40.

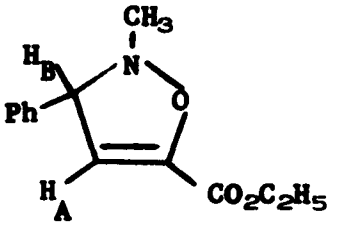
Cyanoacetylene and C-phenyl-N-methylnitrone reacted regioselectively at 50° in benzene to give 2-methyl-3-phenyl-4-cyano-Δ^4-isoxazoline (55a). The structure of 55a is conveniently assigned by a comparison of its nmr spectrum to those of model compounds 55b and 56



a R = C≡N

b R = $CO_2C_2H_5$

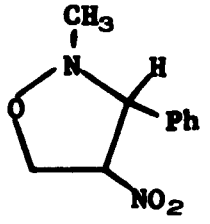
55



56

obtained as a 58:42 mixture of cycloadducts in a similar reaction reported by Huisgen.[31] The absorption of the olefinic proton H_A of 55b is under the absorption of the aromatic protons of the phenyl group and the olefinic proton H_A of 56 is a doublet (J = 3.0 Hz) at δ 5.78. The C-3 protons of 55b and 56 are at δ 4.82 s and δ 4.78 d, respectively. The chemical shifts of the ring protons of 55a are almost identical to those of 55b. The olefinic proton H_A of 55a is at δ 7.10 d and the C-3 proton is a doublet (J = 2.0 Hz) at δ 4.78. The structure assignment of 55a, then, is unambiguous.

Nitroethylene and C-phenyl-N-methylnitrone reacted regioselectively at 60° in chloroform to give a mixture of the cis- and trans-4-substituted isomer, 2-methyl-3-phenyl-4-nitroisoxazolidine (57). The major isomer (74%) in solution was cis-57 [Nmr spectrum ($CDCl_3$): δ 3.87

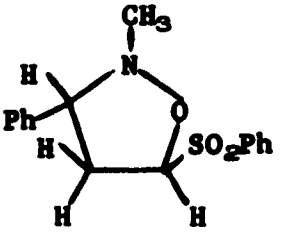


57

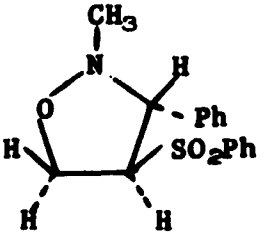
(CHPh, d, J = 8.0 Hz, 1H); ABX octet- δ 4.34(OCHCNO$_2$-trans, dd, J = 8.0, 10.5 Hz, 1H), δ 4.62 (OCHCNO$_2$-cis, dd, J = 5.5, 10.5 Hz, 1H); δ 5.46

($CHNO_2$, ddd, J = 5.5, 8.0, 8.0 Hz, 1H)] while silica gel or added base caused total isomerization to the more stable trans-57 [Nmr spectrum (CCl_4): δ 3.95 (CHPh, d, J = 6.0 Hz, 1H); ABX octet- δ 4.15 (OCHCNO$_2$-trans, dd, J = 6.7, 10.5 Hz, 1H), δ 4.44 (OCHCNO$_2$-cis, dd, J = 3.0, 10.5 Hz, 1H); δ 4.95 ($CHNO_2$, ddd, J = 3.0, 6.0, 6.7 Hz, 1H)].

Phenyl vinyl sulfone reacted with C-phenyl-N-methylnitrone at 80° in $CHCl_3$ to give a 32:68 mixture of the normal adduct (58) and the reversed adduct (59). The normal isomer, 58, was isolated as a cis,trans mixture [Nmr spectrum ($CDCl_3$): δ 5.02 ($OCHSO_2Ph$, dd, J = 3.0, 8.3 Hz, 1H)] which did not undergo deuterium exchange in NaOEt/EtOD after nine days. Only trans-59 was isolated from the reaction mixture. Presumably, silica gel of a plc plate caused isomerization of any cis-59 formed in the reaction to the more stable trans isomer. Deuterium exchange of the C-4 proton of 59 without epimerization was easily effected in $KOH/D_2O/THF$. The nmr spectrum of the undeuterated material has a complex multiplet at 3.60-4.70 ppm for the four ring protons and the nmr spectrum of the deuterated compound has an AB quartet [δ_A 4.25, δ_B 4.47, J_{AB} = 9.5 Hz] for the C-4 protons and a singlet for the benzylic proton at δ 3.87. Nmr spectra of compounds 59 and C-4 deuterated 59 are given in Appendix A.



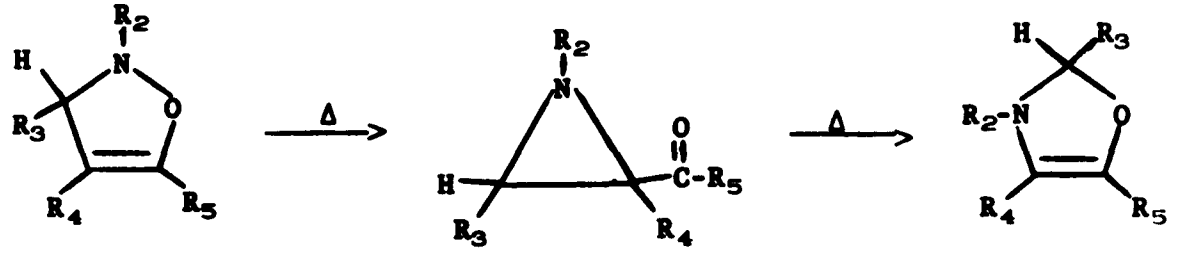
58



59

3. Rearrangements of Δ^4-Isoxazolines

The literature contains few references to the instability of Δ^4-isoxazolines.[46] In some cases, the isolation of rearrangement products have been reported.[47] Baldwin et al.,[46] proposed a mechanism for the thermal rearrangement of Δ^4-isoxazolines to Δ^4-oxazolines (Figure 21) and reported the data given below to support their proposal. The probable intermediacy of an aziridine was shown by the rapid rearrangement of 60 to the isolable acylaziridine, 61. Further heating produced



Δ^4-Isoxazoline I | Acylaziridine II | Δ^4-Oxazoline III

Figure 21. Baldwin's Mechanism for the Rearrangement of Δ^4-Isoxazolines

the Δ^4-oxazoline, 62. The rearrangement of 63 to 65 at 80° was monitored

$$[\text{I}]\ \left[R_2 = 2,4,6\text{-trimethylphenyl},\ R_3 = H,\ R_4 = R_5 = CO_2CH_3\right] \xrightarrow{25^\circ} \text{II} \xrightarrow{110^\circ} \text{III}$$

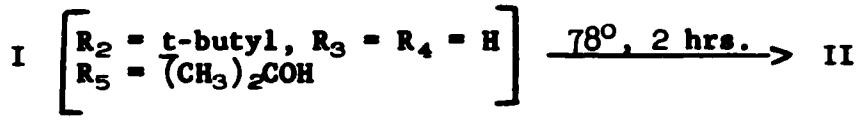
60 61 62

by nmr spectroscopy. Compounds 60 and 63 were obtained from the rapid reactions of N-(2,4,6-trimethylphenyl)nitrone and N-t-butylnitrone with dimethyl acetylenedicarboxylate at 25° and 0°, respectively.

$$\text{I}\ \left[R_2 = \text{t-butyl},\ R_3 = H,\ R_4 = R_5 = CO_2CH_3\right] \xrightarrow{80^\circ} [\text{II}] \xrightarrow{80^\circ} \text{III}$$

63 64 65

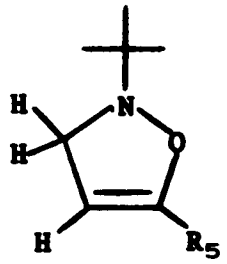
The reaction of N-t-butylnitrone and 3-methylbutyn-3-ol at 74° (10 min) produced the labile isoxazoline 66 which slowly rearranged at 78° to the acylaziridine, 67. The reaction was monitored by nmr spectroscopy.

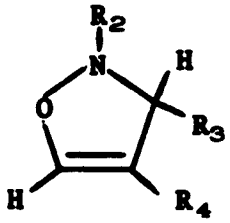


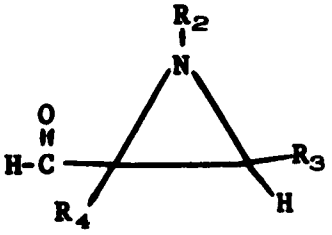
66 67

Product formation and reaction rates for the reactions described above were not influenced by oxygen, radical inhibitors, or small amounts of acids or bases.[46]

The regioisomeric Δ^4-isoxazolines, 68 and 69, synthesized in these studies were observed to have marked differences in stability. The 4-substituted isomers, 69 underwent rearrangement in CCl_4 solutions







70

a) $R_5 = CO_2C_2H_5$

b) $R_5 = C{\equiv}N$

c) $R_5 = Ph$

68

a) R_2 = t-butyl, $R_3 = H$, $R_4 = CO_2C_2H_5$

b) R_2 = t-butyl, $R_3 = H$, $R_4 = C{\equiv}N$

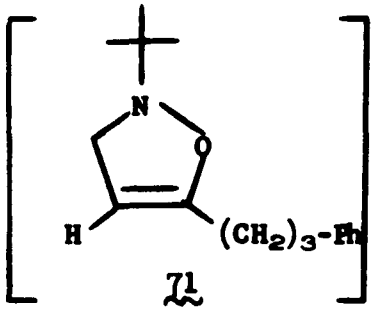
c) $R_2 = CH_3$, $R_3 = Ph$, $R_4 = C{\equiv}N$

69

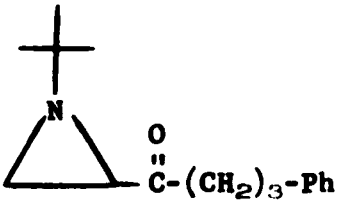
above 80° while the corresponding 5-substituted isomers, 68, were stable under identical conditions. Reactions were carried out in sealed nmr tubes and were followed by nmr spectroscopy. The nmr spectra of all

rearrangement mixtures included a small but constant intensity absorption at δ 9.0-10.0 strongly indicating that rearrangements were occurring to the Δ^4-oxazoline *via* formylaziridines (70). Rearrangement products were not isolated.

Other isoxazoline rearrangements were also observed in these studies. Only the acylaziridine, 72, presumably formed from 71, was isolated in the reaction of *N*-*t*-butylnitrone and 5-phenyl-1-pentyne at 85° in CCl_4. The reaction of *C*,*N*-diphenylnitrone and cyanoacetylene at 35° was monitored by nmr spectroscopy. As the reactants disappeared,



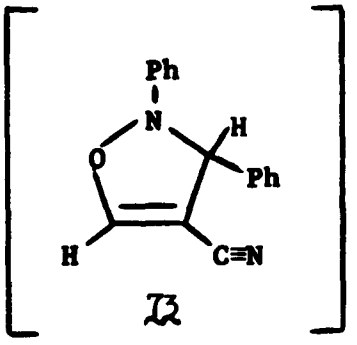
71



72

several new peaks appeared in the nmr spectrum of the reaction mixture the most notable of which was a constant, low intensity singlet at δ 9.96 and a doublet (or two singlets) at δ 9.25. Tlc of the reaction mixture showed several spots. Products were not isolated. Since only the 4-cyano-Δ^4-isoxazolines from other reactions were shown to be unstable, *C*,*N*-diphenylnitrone and cyanoacetylene apparently react to form 2,3-diphenyl-4-cyanoisoxazoline (73) which subsequently rearranges to aziridines and Δ^4-oxazolines.

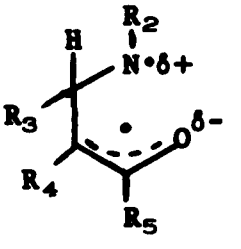
Baldwin[46] has attributed the difference in the propensity for rearrangement of isoxazolines 60, 63, and 66 to differences in the ease of N-O bond cleavage. This explanation satisfactorily rationalizes the difference in reactivity observed for 68 and 69 in these studies, since



73

⟶ Aziridines ⟶ Oxazolines

an intermediate (or concerted transition involving simultaneous C-N bond formation) of the type 74 would be substantially stabilized by a substituent at C-4, but only slightly by substitution at C-5. Electron withdrawing or conjugating substituents on C-4 and/or electron releasing or conjugating substituents on nitrogen will be particularly effective if some polarization of the transition state occurs as in 74.



74

Apparently, 5-substituted Δ^4-isoxazolines readily undergo rearrangements if the C-5 substituent is an electron-releasing group as in 71. Further studies are necessary before these rearrangements can be fully understood. Particularly, a knowledge of the propensity of Δ^4-isoxazolines with only electron releasing substituents on C-4 and C-5 and with a combination of electron-withdrawing and electron-releasing substituents on C-4 and C-5 to undergo rearrangements would be helpful in fully understanding the observations reported here.

PART C Reactions of Nitrones with Fulvenes

No reactions of nitrones and fulvenes have been reported in the literature. The thermally allowed 1:1 cycloadducts of 1,3-dipoles and fulvenes are shown in Figure 1 (Section I A). Four [4+2] adducts (two pairs of regioisomers) and two regioisomeric [6+4] adducts are possible. "Periselectivity" refers to selectivity in formation of one of these thermally allowed products. Simple fulvenes are ideal compounds for periselectivity studies, since they are reactive (highly perturbed) trienes having only slightly differing steric requirements for different modes of reaction. The reactions of nitrones and fulvenes carried out in these studies were periselective and in accord with predictions of frontier orbital theory.

The frontier orbital energies of fulvene, two 6,6-disubstituted fulvenes, and N-t-butylnitrone are shown in Figure 22. The changes in the frontier orbital energies of fulvene associated with C-6 mono and disubstitutions were discussed in Section II A. The HO orbital energies of the nitrone and fulvenes were determined experimentally and the LU orbital energies were estimated from absorption spectra or calculations[10,41] (Section II A). The interactions between the frontier orbitals of N-t-butylnitrone and the fulvenes shown in Figure 22 are similar to the frontier orbital interactions of N-t-butylnitrone and conjugated dipolarophiles and both kinds of reactions are LU, HO controlled. Arguments about reactivity for reactions of nitrones and fulvenes follow those given earlier for alkenes and alkynes (Section II B).

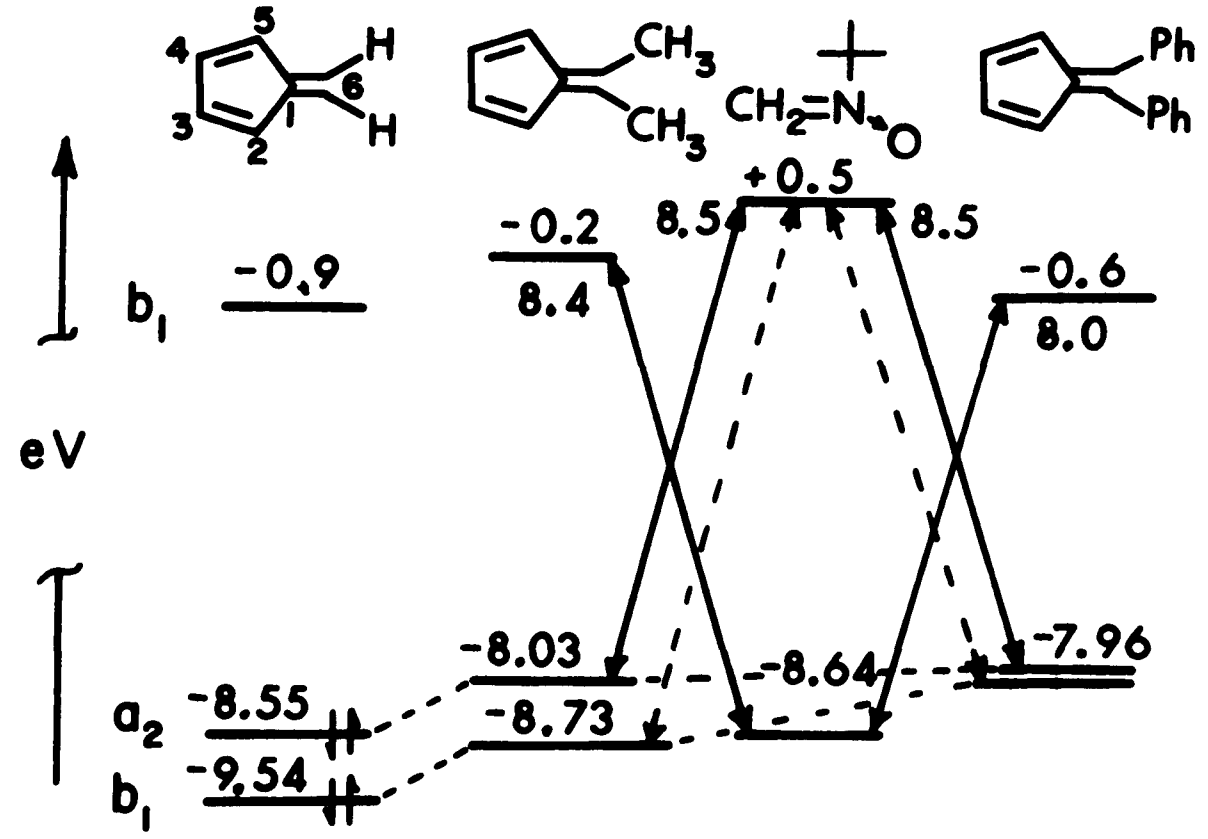


Figure 22. Frontier Orbital Energies of Fulvenes and N-t-Butylnitrone

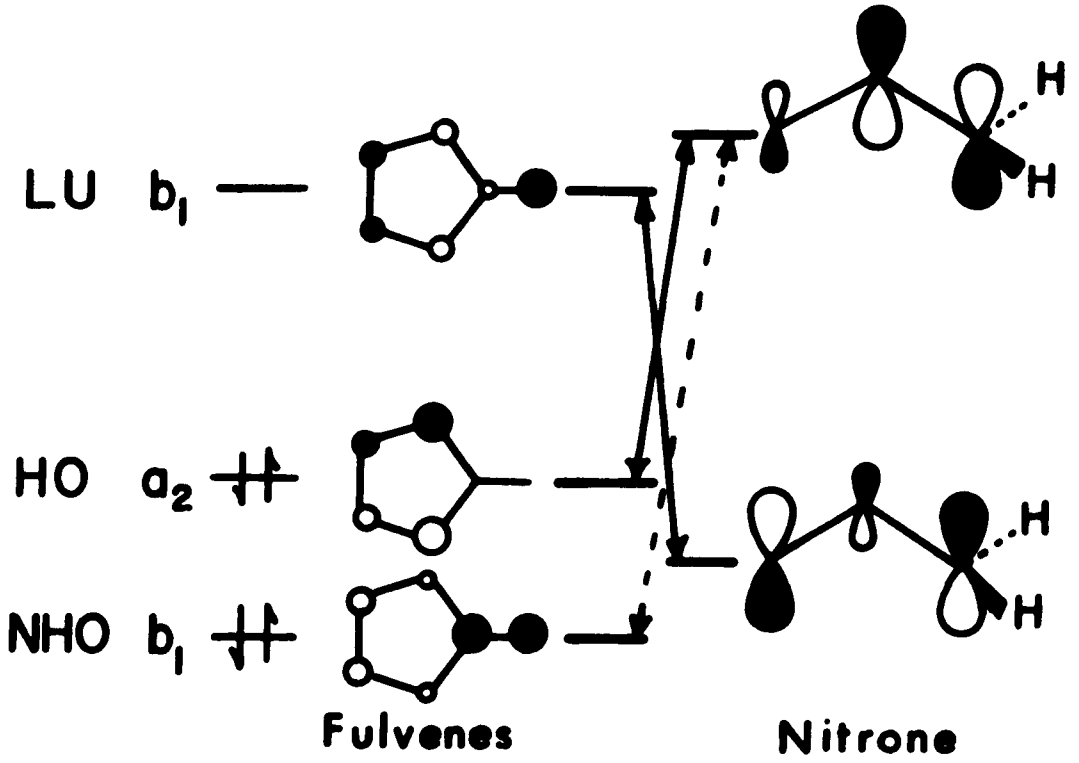
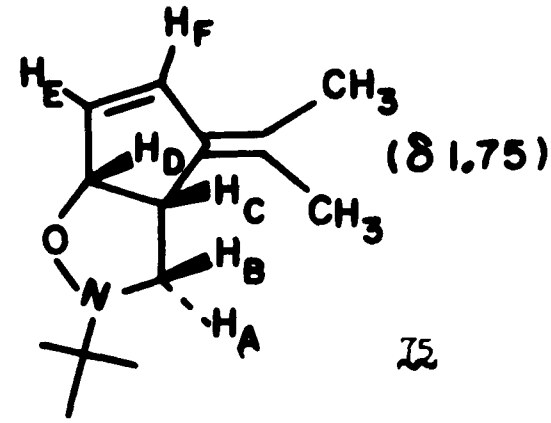


Figure 23. Frontier Orbital Interactions of Fulvenes and N-t-Butylnitrone

The frontier orbital interactions of nitrones and fulvenes are shown in Figure 23. Orbital energies and relative magnitudes of frontier orbital coefficients of nitrones and fulvenes were discussed in Section II A. For concerted cycloadditions of nitrones to fulvenes, the favored regioisomer and periisomer will be that in which the largest coefficients in each of the interacting frontier orbitals are united, i.e., regioselectivity and periselectivity are controlled by the same interactions. The product(s) formed in these reactions depend upon the relative dispositions of the frontier orbitals of the nitrone and fulvene and upon the relative positions of the a_2 and b_1 HO and NHO orbitals (Figure 23). An analysis of the results obtained in these studies will illustrate the application of these ideas.

N-t-butylnitrone reacted with dimethylfulvene at 70° in CCl_4 to give a 54% yield of the 1:1 adduct, 75. The structure of this product is consistent with mass spectral data (M^+ = 207) and the nmr data given. Two minor fractions were also isolated. Although structure assignments were not made for these products, mass spectral data M^+ = 308) and nmr data (no olefinic protons) indicated that they were 2:1 adducts. The methyl proton resonances of each of the three fractions were at δ 1.6-1.8 indicating that no addition had occurred across the exocyclic double bond of the fulvene.

The formation of 75 can be rationalized by frontier orbital concepts. Both pairs of frontier orbital interactions of N-t-butylnitrone and dimethylfulvene are similar (Figure 22). However, the coefficients of the HO orbital of N-t-butylnitrone are approximately equal (Section II A) and product formation is controlled by the nitrone LU - fulvene HO interactions. Union of the larger coefficients for this



75

(δ 1.20 s)

δ_A 2.39 dd, J = 7.9, 5.1 Hz

δ_B 2.98 dd, J = 7.9, 7.9 Hz

δ_C 3.38 ddd, J = 5.1, 7.9, 6.7 Hz

δ_D 4.92 dd, J = 6.7, 2.6 Hz

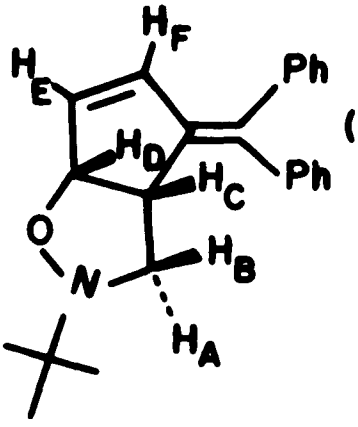
δ_E 5.77 dd, J = 5.6, 2.6 Hz

δ_F 6.38 d, J = 5.6 Hz

(The nmr spectrum of 75 is included in Appendix A.)

interaction gives only the thermally allowed product 75 (Figure 23). The NHO orbital of dimethylfulvene is sufficiently low in energy (0.7 eV lower than HO) that it does not influence product formation. Formation of the [6+4] adduct through interaction of the nitrone HO - fulvene LU is less favorable than the formation of 75 in part because of steric hindrance at the C-6 position of the fulvene, but also because both pairs of frontier orbital interactions stabilize the transition state leading to 75, while only the nitrone HO - fulvene LU interaction stabilizes the [6+4] transition state.

N-t-Butylnitrone reacted with diphenylfulvene at 70° in CCl_4 to give the 1:1 adducts 76 (67%) and 77 (14%). The structures of these products are consistent with mass spectral data (M^+ = 331) and the nmr data given. A third fraction consisting of several components was also isolated from the reaction mixture. Although structure assignments were not made for these products, nmr data of the mixture (no olefinic protons) indicated that the components are the 2:1 nitrone:fulvene adducts.



(δ 7.18m)

(δ 0.98s)

76

δ_A 2.40 dd, J = 9.0, 5.6 Hz

δ_B 2.60 dd, J = 9.0, 7.6 Hz

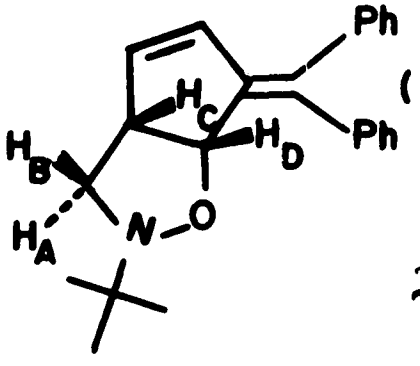
δ_C 3.7 ddd, J = 7.1, 5.6, 7.6 Hz

δ_D 4.97 dd, J = 2.6, 7.1 Hz

δ_E 5.97 dd, J = 5.6, 2.6 Hz

δ_F 6.48 d, J = 5.6 Hz

(The nmr spectra of compounds 76 and 77 are included in Appendix A.)



(δ 7.18)

(δ 1.10s)

77

δ_A 2.52 dd, J = 8.0, 4.5 Hz

δ_B 2.98 dd, J = 8.0, 8.0 Hz

δ_C 3.62 m, J = 8.0, 4.5, 2.1, 6.0 Hz

δ_D 4.58 d, J = 6.0 Hz

δ_E 5.82 d, J = 2.1, 5.6 Hz

δ_F 6.22 m, J = 5.6 Hz

$J_{CF} \approx 1.0$ Hz

The formation of 76 and 77 is also consistent with frontier orbital concepts. Both pairs of frontier orbital interactions of N-t-butylnitrone and diphenyl fulvene are similar (Figure 22). The fulvene "HO" and "NHO" energies are approximately the same. The coefficients of the HO orbital of N-t-butylnitrone are approximately equal (Section II A) and product formation is controlled by the nitrone LU - fulvene HO and NHO interactions. Union of the larger coefficients of the nitrone LU and the fulvene HO gives the thermally allowed product 76 (Figure 23).

Union of the larger coefficient of the nitrone LU and the larger ring coefficient (C-3 or C-4) of the fulvene NHO gives the thermally allowed product 77. Formation of the [6+4] adduct through interaction of the nitrone LU - fulvene NHO or through interaction of the nitrone HO - fulvene LU is apparently unfavorable because of steric hindrance at the C-6 position of the fulvene.

Reaction of N-t-butylnitrone with 6-methyl-6-phenylfulvene (78) and the reactions of C-phenyl-N-methylnitrone with dimethyl- and diphenylfulvene were also carried out in these studies. The structures of isolated products were not assigned. However, nmr data for the 1:1 adducts indicate that only the thermally allowed [4+2] cycloadducts are formed in agreement with frontier orbital theory.

PART D Summary and Conclusions

A recent application of perturbation theory to 1,3-dipolar cycloaddition reactivity, regioselectivity, and periselectivity has provided a rationalization of these phenomena.[10] Results of the work reported here confirm these ideas for the reactions of nitrones with alkenes, alkynes, and fulvenes. Nitrone reactivities in cycloadditions were shown to be related to the relative disposition of the interacting frontier orbitals, and regioselectivity and periselectivity were shown to be related to the coefficients of the interacting frontier orbitals.

Most monosubstituted alkenes and alkynes react with nitrones to give only the 5-substituted isoxazolidines and isoxazolines. The dominant frontier orbital interaction of nitrones and electron-rich alkenes and alkynes is dipole LU - dipolarophile HO and regiochemistry is controlled by the terminal coefficients of the dipole LU and dipolarophile HO orbitals. Only the 5-substituted isomers are formed. Both pairs of frontier orbital interactions are important in reactions with conjugated dipolarophiles; however, since the terminal coefficients are similar for the HO orbital of nitrones, regiochemistry is controlled by the dipole LU orbital. The dominant frontier orbital interaction with electron-deficient dipolarophiles is dipole HO - dipolarophile LU; again, as with conjugated dipolarophiles, regiochemistry is controlled by the nitrone LU orbital. For very electron-deficient monosubstituted alkenes of I.P. $\geq$ 11.2 eV, the dipole HO - dipolarophile LU frontier orbital interaction is sufficiently great that partial or total reversal of regioselectivity (formation of 4-substituted isomer) with nitrones is

observed. Reactions of the sterically unencumbered N-t-butylnitrone demonstrate that regioselectivity is controlled by electronic and not steric factors.

The periselectivity of N-t-butylnitrone reactions with 6,6-diphenyl- and 6,6-dimethylfulvene was also shown to be in accord with frontier orbital concepts. Two of the thermally allowed cycloadducts ([4+2]) were observed with diphenylfulvene and only one thermally allowed cycloadduct ([4+2]) was observed with dimethylfulvene. The formation of all three products was controlled by the nitrone LU - fulvene HO or NHO orbital interactions.

In general, the successful application of perturbation theory for rationalizing and predicting regioselectivity and periselectivity of nitrone cycloadditions has been demonstrated. Frontier orbital theory could be applied more quantitatively if more accurate data for frontier orbital energies, especially LU energies, and frontier orbital coefficients were available.

III. EXPERIMENTAL

PART A General Information

Preparation of starting materials and syntheses of new compounds described here utilized solvents and reagents of commercial reagent grade.

Microanalyses were performed by Ralph Seab, Louisiana State University, Baton Rouge.

Melting points were determined on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected.

Mass spectra (ms) were determined by Paula B. Watts and Paul J. Moses on a Hitachi Perkin-Elmer Model RMS-4 Mass Spectrometer using an ionization energy of 70 eV. In general, only parent peaks (M^+) and m/e ratios for peaks with intensities greater than 15% of the base peak are given.

Infrared spectra (ir) were recorded on a Perkin-Elmer Infracord Model 137. The 3.30 and 6.24 μ bands of polystyrene were used as calibration standards.

Nuclear magnetic resonance spectra (nmr) were recorded on a Perkin-Elmer Model R12B (60 MHz) Spectrometer. Double resonance studies were also carried out on this instrument. Chemical shifts are reported in ppm (δ) and the usual notations are used to describe the spectra, i.e., s = singlet, d = doublet, m = multiplet, b = broad, etc.

Electronic spectra (uv) were determined on a Cary 14 Spectrometer.

Diazomethane used in the synthesis of N-t-butylnitrone was prepared from Diazald utilizing an Aldrich Chemical Company Diazald Kit for the generation of diazomethane.

Specific information related to the data in Parts C and D is given at the beginning of these Sections.

PART B Starting Materials

1. Synthesis of Nitrones

Nitrone syntheses were recently reviewed.[18]

a. Synthesis of N-Methylene-t-Butylamine N-Oxide (N-t-Butylnitrone)

An overall scheme for the synthesis of N-t-butylnitrone from t-butylamine is outlined in Section I B. The procedure outlined here gives optimum yields of the nitrone in carbon tetrachloride solution.

Ten milliliters of chloroform were added to 7.27 g (0.08 mol) of t-nitrosobutane dimer in a 500 ml flask. The royal blue color of the nitroso-monomer rapidly appeared. Diazomethane (6.75 g, 0.16 mol) generated from Diazald[48] and codistilled with diethyl ether (~ 450 ml) was condensed directly into the t-nitrosobutane solution cooled in an ice bath. The mixture was allowed to warm up to room temperature and stand for eight hours with continuous stirring. Excess diazomethane was removed by blowing a stream of dry nitrogen over the swirling surface of the ethereal solution. The product was concentrated at reduced pressure to ~ 100 ml, and 200 ml of CCl_4 were added. Again, solvent was removed at reduced pressure to afford a 27 g carbon tetrachloride solution of N-t-butylnitrone (2.1 mmol/g sol'n, 68% yield). The nitrone, reported as a colorless oil,[3c,d] was used in solution and not isolated in pure form. Concentrations were determined by nmr spectroscopy using benzene as a standard.

Nmr spectrum (CCl_4): δ 1.47 ppm, s, 9H; AB pattern, δ_A 6.46, δ_B 6.34, J_{AB} = 7.5 Hz. On fourfold dilution to 0.30 mmol/g sol'n, the AB pattern collapsed into a singlet. Nmr spectrum (D_3COD): δ 1.49, s, 9H; AB pattern, δ_A 6.77, δ_B 6.61, J_{AB} = 6.4 Hz.

Preparation of 2-Methyl-2-Nitrosopropane (t-Nitrosobutane).

Approach 1. Hypobromite Oxidation of t-Butylhydroxylamine. This procedure is very similar to that of Emmons.[21a] An 8.9 g (0.10 mol) quantity of t-butylhydroxylamine in 75 ml of water was added dropwise over a ten-minute period with efficient stirring to an ice cooled solution of 19.2 g (0.12 mol) of bromine and 12.0 g (0.30 mol) of sodium hydroxide in 75 ml of water. A blue color immediately developed. The mixture was stirred for 3 hr. at 0°, and the colorless crystalline dimer was collected on a filter and dried at room temperature and 0.5 mm pressure (7.3 g, 84% yield). The compound melted (sealed tube) at $75\text{-}76^{\circ}$ (lit.[21a] $83\text{-}84^{\circ}$; lit.[49] 76°). The nmr spectrum in CCl_4 has singlets at δ 1.24 ppm and δ 1.56 ppm with integrated intensities of 16:7. On fourfold dilution the integrated intensities were 16:3. Consequently, the high and low field singlets are assigned to the monomer and dimer, respectively.

Approach 2. m-Chloroperbenzoic Acid Oxidation of t-Butylhydroxylamine. Holman and Perkins[50] recently reported this ingenious "no solvent" synthesis which provides a convenient route to t-nitrosobutane uncontaminated with t-butylhydroxylamine. N-t-Butylnitrone prepared from this amine-free t-nitrosobutane is especially desirable for reactions with alkenes that are susceptible to base initiated polymerizations.

A mixture of 45 g (0.22 mol) of commercial m-chloroperbenzoic acid (85%) and 456 g of sodium chloride was packed in a glass tube (2.5 cm ID X 74 cm) fitted with fritted glass plugs on both ends and wrapped with a cooling jacket. Cooling fluid at -3° was circulated through the jacket to maintain the inside temperature between $0\text{-}5^{\circ}$.

Dry nitrogen was slowly bubbled through t-butylamine (18.0 g, 0.25 mol) which was cooled in an ice bath. The nitrogen-t-butylamine gas stream was forced through the reaction tube, and the effluent gases were directed through two collecting tubes in series cooled to -80°. Nitrogen from the second collecting tube exit was bubbled through a column of oil to monitor the gas stream flow rate. A blue product immediately appeared in the first collecting tube. After 8 hrs the nitrogen flow was stopped and the collecting tubes were stored at -80°. After two days, some blue color persisted. Cold water was added to the product and the collecting tubes were stored in an ice bath for 3 hrs. The crystalline dimer was collected on a filter and dried at reduced pressure (0.5 mm) for 20 minutes. Yield, 2.39 g, 22% (lit.[50] 0.31 g, 49%).

Preparation of t-Butylhydroxylamine

To a vigorously stirred mixture of 99.5 g (0.97 mol) of t-nitrobutane and 120 g (2.22 mol) of NH_4Cl in 650 g of water was slowly added 130 g (2.00 mol) of zinc dust over a 45-minute period. A water bath was used to maintain the temperature of the rapid and exothermic reaction between 45° and 55°. The reaction mixture was filtered and the residue was washed several times with water. The aqueous filtrate (~ 1000 ml) was subjected to continuous extraction with diethyl ether for seven days.[51] Removal of the ether at reduced pressure afforded 75.5 g (75% yield) of t-butylhydroxylamine, mp = 56-62° (lit.[51] 64-65°). Nmr spectrum ($CDCl_3$): δ 1.11 ppm, s, 9H; δ 6.22, bs, 2H.

Preparation of t-Nitrobutane

The procedure of Kornblum et al.,[52] was followed verbatim to synthesize 99.5 g (71% yield) of t-nitrobutane by oxidation of t-butylamine (MCB, bp 44-45°) with potassium permanganate.

b. Synthesis of C-Phenyl-N-Methylnitrone

C-Phenyl-N-methylnitrone is conveniently prepared by the condensation of methylhydroxylamine and benzaldehyde.[53] Isolation of methylhydroxylamine from a Beckmann reduction of nitromethane[54] is exceedingly difficult. A procedure was developed for the synthesis of C-phenyl-N-methylnitrone from nitromethane and benzaldehyde in which methylhydroxylamine is not isolated.

To 100 g (1.64 mol) nitromethane, 60 g (1.12 mol) of NH_4Cl, and 800 g of water, 275 g (4.20 mol) of zinc dust was added in small quantities over a two-hour period. The product was filtered and the residue was washed several times with water. The filtrate (~ 800 ml) was adjusted from pH 9 to pH 2 with conc. HCl. The acidic solution was concentrated at reduced pressure and 50° to a final volume of ~ 50 ml. The pH of the hydroxylamine hydrochloride solution was made slightly basic with conc. NH_4OH and the resulting solution was added slowly at room temperature to 26.0 g (0.25 mol) of benzaldehyde suspended in 140 ml of a 2N NaOH solution. The product was extracted with chloroform and the solvent was removed at reduced pressure. On cooling, 28.2 g (85% yield) of C-phenyl-N-methylnitrone crystallized from the residue. Recrystallization from benzene-petroleum ether (30-60°) gave almost colorless crystals, mp 74-78°, (lit.[53] 82°). Sublimation of the product at 70° and 0.5 mm increased the melting point to 81-83°. The nmr spectrum of C-phenyl-N-methylnitrone has been described in the literature.[55] Anal. Calcd. for C_8H_9NO: C, 71.08; H, 6.72; N, 10.36. Found: C, 71.03; H, 6.70; N, 10.38.

c. Synthesis of C,N-Diphenylnitrone

C,N-Diphenylnitrone was prepared by the condensation of phenylhydroxylamine and benzaldehyde as described by Wheeler and Gore.[56]

2. Synthesis of Alkenes and Alkynes

Commercially available alkenes and alkynes were used in these studies without further purification.

a. Preparation of Nitroethylene

The procedure of Buckley and Scaife[57] for the dehydration of 2-nitroethanol with phthalic anhydride was followed verbatim. Five grams of 2-nitroethanol (Aldrich, bp 60° at 0.5 mm) was converted in 36% yield to nitroethylene, bp 40° at 80 mm.

b. Preparation of 1-N-Pyrrolidino-1-Cyclopentene

Herr and Heyl[58] have described a general scheme for the preparation of enamines. The following procedure is an adaptation of their method.

A mixture of 100 ml of benzene, 21.3 g (0.30 mol) of pyrrolidine, 16.8 g (0.20 mol) of cyclopentanone, and 41.5 g (0.30 mol) of anhydrous K_2CO_3 was refluxed under nitrogen with stirring for 6 hrs. The solid was removed by filtration and the solvent and excess amine were removed by flash evaporation. Distillation of the residue at 3.2 mm gave 19.2 g (70% yield) of crude 1-N-pyrrolidino-1-cyclopentene, bp 75-80°. A second distillation gave a colorless oil as the major fraction, bp 69-70° at 2.5 mm. The enamine is exceedingly air sensitive and develops a yellow color on brief contact with air.

c. Preparation of Phenyl Vinyl Sulfone

Phenyl vinyl sulfone was prepared by the oxidation of phenyl vinyl sulfide with hydrogen peroxide in acetic acid in 48% yield by the method of Parham *et al.*[59] The sulfone is a white powder, mp 65-67° (lit.[59] 66.5-68°).

Preparation of Phenyl Vinyl Sulfide from β-Chloroethyl Phenyl Sulfide.

Parham *et al.*,[59] reported, without experimental details, an 84% yield for this reaction using KOH in ethanol. Methyl vinyl sulfone has been synthesized in 50% yield in a similar dehydrohalogenation with sodium metal in *n*-amyl alcohol.[60] Potassium t-butoxide in DMSO was found to be a more efficient medium for this reaction.

A 37.2 g (0.22 mol) quantity of β-chloroethyl phenyl sulfide was added dropwise to a stirred solution of 25.0 g (0.22 mol) of potassium *t*-butoxide in 200 ml of DMSO at room temperature over a period of 20 minutes. The reaction was very exothermic. After stirring for another 25 minutes, the reaction mixture was poured into 600 ml of ice water and stirred briefly. The oily product was extracted from the aqueous phase with pentane and the combined pentane extracts (~ 800 ml) were subsequently extracted with water to remove any residual DMSO. The pentane solution was dried over anhydrous Na_2SO_4 and the solvent was removed at reduced pressure. Distillation of the crude product at 2.9 mm pressure and 61° gave 26.5 g (0.19 mol, 88% yield) of phenyl vinyl sulfide.

Preparation of β-Chloroethyl Phenyl Sulfide

β-Chloroethyl phenyl sulfide (bp 64.5-70° at 0.35 mm) was prepared in 84% yield from β-hydroxyethyl phenyl sulfide by the procedure of Bennett and Berry.[61a] β-Hydroxyethyl phenyl sulfide was prepared in quantitative yields from the reaction of thiophenol and 2-chloroethanol.[61b]

d. Preparation of 1-N-Morpholino-1-cyclohexene

1-N-Morpholino-1-cyclohexene (bp 70-72° at 0.60 mm) was prepared in 60% yield by the method of Domschke.[62]

e. Preparation of Vinylidene Cyanide

Vinylidene cyanide was prepared by the pyrolysis of 1,1,3,3-tetracyanopropane as described by Ardis et al.[63] 1,1,3,3-Tetracyanopropane (mp 138-141°; lit.[64] 136-137°) was synthesized in 61% yield from malononitrile and aqueous formaldehyde as described in the literature.[64]

f. Preparation of Deuterocyanoacetylene

A 150 mg quantity of cyanoacetylene* was shaken with 1.0 g of D_2O for 5 minutes. The product was recovered by flash distillation at room temperature and reduced pressure and collected in a receiving tube cooled to -80°. A second similar distillation was performed to remove D_2O. The product was 74% deuterated as determined by a comparison of the nmr spectra of standard solutions of cyanoacetylene and deuterocyanoacetylene.

*Purchased from Terra-Marine Bioresearch, P. O. Box 2208, La Jolla, California 92037.

3. Synthesis of Fulvenes

The syntheses of fulvenes were reviewed in 1968.[11] 6,6-Diphenylfulvene,[65a] 6,6-dimethylfulvene,[65b] and 6-methyl-6-phenylfulvene[65a] were synthesized by the base-catalyzed condensations of cyclopentadiene with the appropriate ketone.

a. Preparation of 6,6-Diphenylfulvene

Twenty-two grams (0.34 mol) of freshly distilled cyclopentadiene were added slowly to a solution of sodium ethoxide (prepared from 8.0 g of sodium metal and 240 ml of absolute ethanol) containing 57.6 g (0.32 mol) of benzophenone. After addition was completed, the red solution was heated on a steam bath for 10 minutes. On cooling slowly to 0°, orange-red crystals separated. The product was filtered off and recrystallized from absolute ethanol. Yield: 47%, mp 81-82° (lit.[65a] 82-82.5°).

b. Preparation of 6,6-dimethylfulvene

Five moles of acetone and five moles of freshly distilled cyclopentadiene were placed in a round-bottom flask fitted with a reflux condenser and cooled with ice. One hundred milliliters of a 20% solution of potassium hydroxide in ethanol was added with an addition funnel. When the vigorous reaction was completed, the flask was stoppered and stored at 0° for 10 hrs. The water layer was separated and the low boiling materials was removed at reduced pressure. The major fraction of dimethylfulvene was collected at 48-51° and 10 mm pressure. Yield, 41%.

c. Preparation of 6-Methyl-6-Phenylfulvene

6-Methyl-6-phenylfulvene was prepared by the base-catalyzed condensation of cyclopentadiene and acetophenone in 57% yield using the same procedure used for dimethylfulvene.

PART C Cycloadditions with Alkenes and Alkynes

Preparative scale cycloadditions were carried out in sealed test tubes under nitrogen in ~ 3 ml. of solvent. Optimum reaction temperatures and times were determined from small scale reactions carried out in sealed nmr tubes under nitrogen and monitored by nmr spectroscopy.

Preparative (plc) and thin layer (tlc) chromatography were performed on glass plates and aluminum sheets, respectively, coated with EM Reagents Silica Gel F-254. The eluent consisted of X% ethyl acetate in cyclohexane, v/v. Selected fractions were scraped from the plc plates and eluted with ethyl acetate. The desired fraction(s) were identified by nmr spectroscopy and, for most reactions, subsequently purified further by preparative layer chromatography. Separation data for each plc purification is reported as (X%, Y elutions).

Many compounds isolated by preparative layer chromatography had no uv adsorptions above 200 nm and could not be seen on a plc plate with an ultraviolet light. These sample fractions were identified by exposing a two-to-three centimeter strip of the plc plate in an iodine developing tank for twenty-to-thirty minutes. Since the exposed portion of the plate had to be discarded, yields for these reactions were necessarily reduced by five-to-fifteen percent.

Reactivities and relative reactivity orders for reactions of dipolarophiles with nitrones were sought. Bimolecular rate constants were determined by monitoring small scale reactions with nmr spectroscopy. All reactions employed equal concentrations of reactants (~ 0.75 mmol) in approximately one milliliter of solvent sealed in nmr tubes under nitrogen. For studies above room temperature, the reaction

mixture was heated in an oil bath (± 0.3° C), periodically removed and rinsed with acetone to quench the reaction and clean the nmr tube, and the nmr spectrum was recorded. The concentrations of reactants were assumed to be directly proportional to the peak height of the methylene proton singlet of N-t-butylnitrone (6.0-7.0 ppm) or the methyl proton singlet of C-phenyl-N-methylnitrone (3.0-5.0 ppm). Three or more spectra for the first half-life of each reaction were recorded. Data were obtained in most cases for only one sample of a given reaction.

Reaction solvents, temperatures, calculated enthalpies, and extrapolated rate constants for N-t-butylnitrone and C-phenyl-N-methylnitrone cycloadditions are reported and discussed in Section II B.

A complete description of the experimental procedure is given for the preparative scale cycloaddition of methyl acrylate and N-t-butylnitrone. The procedures for the remaining reactions were similar and the experimental details and product data are summarized in Tables XVIII-XX. Other cycloadditions and related reactions are described separately. Data summarized in tabular form are cross referenced with related data in this unit and with related discussions in Section II B.

In general, only four kinds of compounds were synthesized in these reactions: 4- and 5-substituted isoxazolidines and 4- and 5-substituted isoxazolines. Representative nmr spectra for each of these kinds of compounds are included in Appendix A. Detailed descriptions of the nmr spectra of all new compounds are given.

1. Cycloadditions

Reaction of Methyl Acrylate and N-t-Butylnitrone

Experimental Details for a Representative Cycloaddition Reaction.

A 0.27 g (3.1 mmol) quantity of methyl acrylate and 2.30 g (3.1 mmol) of N-t-butylnitrone solution (CCl_4, 1.3 mmol/g sol'n) were mixed in a test tube at room temperature and left standing under nitrogen for 3 hrs. Tlc of the reaction mixture (75%, 1 elution) revealed only one spot (Iodine development), R_f = 0.30. The entire reaction mixture was placed on a 20 x 40 cm plc plate and eluted once with 100% ethyl acetate. An approximately 2.5 cm strip of one end of the plc plate was exposed for 30 minutes in an iodine developing tank. The desired fraction (excluding the iodine stained portion) was scraped from the plate and the product was extracted with ethyl acetate (~ 125 ml). The solvent was removed at reduced pressure and the product was purified further by short-path distillation.

See Tables XVIIIA-XVIIIC for a summary of additional data for this reaction and nmr spectrum No. 42 of Appendix A.

Notes: 1) Most products separated from the reaction mixture by preparative layer chromatography were placed on another plc plate for additional purification followed by short-path distillation.

2) For the very exothermic reaction of cyanoacetylene with N-t-butylnitrone, the reactants were mixed at 0° and allowed to slowly warm up to room temperature. Reactants were mixed at room temperature for all other cycloadditions listed in Tables XVIIIA-XXA.

TABLE XVIIIA

REACTIONS OF N-t-BUTYLNITRONE WITH ALKENES: SYNTHESIS OF ISOXAZOLIDINES

A = 5-Substituted Isoxazolidines; B = 4-Substituted Isoxazolidines

Cross Ref.[1]	Product	Yield(%)	Nitrone (mmol)	Alkene (mmol)	Reaction Conditions[2]	Plc Separation[3] Detection Eluent Elutions	Distillation Temp. & Pressure[4] or mp
[87]	CH_2=$CHCO_2CH_3$ A	78	3.1	3.1	CCl_4, 25°, 3.0 hrs.	(100%, 1) I_2	52°, 1.0 mm Hg
[87]	CH_2=CHC≡N A	72	3.0	3.0	CCl_4, 25°, 1.0 hrs.	(85, 2) I_2 (30, 3) I_2	55°, 0.8 mm
[87]	CH_2=$C(CH_3)CO_2CH_3$ A	58	3.0	3.1	CCl_4, 25°, 2.0 hrs.	(50, 1) I_2	30°, 1.0 mm
[87]	CH_2=C(OAc)C≡N A	79	3.3	3.1	CCl_4, 50°, 2.0 hrs.	(60, 1) I_2 (50, 2) I_2	94°, 0.6 mm
[87]	CH_2=$C(CH_3)$C≡N A	72	3.1	3.2	CCl_4, 50°, 1.0 hr.	(80, 1) I_2 (50, 2) I_2	45°, 0.7 mm
[93]	CH_2=$CHSO_2Ph$ (products could not be separated by plc) A	98	3.0	3.0	$CHCl_3$, 50°, 1.0 hr.	(75, 1) uv	
	A	70				Cryst. from Diethyl Ether-Pet.Ether(90°-120°)	mp 91-93°
	B	30				Isolated in 67% purity by Fractional Cryst. of A.	

TABLE XVIIIA (Continued)

[87]	$CH_3CH{=}CHCHO$ (trans)		49	3.5	3.8	CCl_4, 80° 2.0 hrs.	(50, 3)	I_2	
		A	53				(50, 2)	I_2	<25°, 0.7 mm
		B	47				(50, 2)	I_2	34°, 0.7 mm
[84]	$CH_2{=}CHPh$	A	73	3.0	3.0	CCl_4, 70° 2.0 hrs.	(100, 1) (100, 1)	uv uv	70°, 0.9 mm
[81]	$CH_2{=}CH{-}S{-}Ph$	A	96	3.2	3.1	CCl_4, 85° 2.0 hrs.	(50, 1) (35, 1)	uv uv	96°, 0.7 mm
[81]	$CH_2{=}CH{-}O{-}CH_2CH(CH_3)_2$	A	61	3.2	3.3	CCl_4, 80° 3.0 hrs.	(75, 2) (75, 2)	I_2 I_2	38°, 0.6 mm
[87]	$CH_3CH{=}CHCO_2CH_3$ (trans)		67	3.0	3.0	CCl_4, 80° 4.0 hrs.	(20, 5)	I_2	
		A	40						40°, 0.8 mm
		B	60						45°, 1.0 mm
[81]	$CH_2{=}CH{-}O{-}Ac$	A	46	3.5	3.8	CCl_4, 80° 3.0 hrs.	(100, 1) (100, 1)	I_2 I_2	49°, 0.7 mm
[87]	$PhCH{=}CHCO_2CH_3$ (trans)		89	3.6	3.0	CCl_4, 86° 6.5 hrs.	(30, 2) (25, 2)	uv uv	115°, 0.7 mm
	(Products could not be isolated on plc)	A	31				Mixture not separated; product ratios determined by nmr.		
		B	69						

TABLE XVIIIA (Continued)

[81]	CH_2=CH(CH_2)$_2$Ph	A	87	3.5	3.2	CCl_4, 80° 12.0 hrs.	(75, | 1)	uv	105°, 0.6 mm
[84]	CH_2=C(CH_3)Ph	A	72	3.8	3.6	CCl_4, 85° 7.0 hrs.	(80, | 1)	uv	68°, 0.6 mm
							(25, | 2)	uv	
[84]	CH_3CH=CHPh (trans)	A	46	4.0	3.2	CCl_4, 130° 2.0 hrs.	(50, | 1)	uv	59°, 0.6 mm
							(90, | 1)	uv	

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, [84] refers to page 84.

2. All reactions were carried out in ~ 3 ml. of solvent.

3. Separations were carried out on plc plates (EM Reagents Silica Gel-F254). The eluent was X% ethyl acetate in cyclohexane, v/v. Each set of data in parentheses for a given reaction refers to separation on a separate plc plate.

4. The final step in the purification of liquids was short-path distillation. The temperature of the oil bath and the distillation pressure are reported.

TABLE XIXA

REACTIONS OF C-PHENYL-N-METHYLNITRONE WITH ALKENES AND ALKYNES

A = 5-Substituted Isoxazolidines; B = 4-Substituted Isoxazolidines; C = 4-Substituted Isoxazoline

Cross Ref.[1]	Product	Yield(%)	Nitrone (mmol)	Alkene (mmol)	Reaction Conditions[2]	Plc Separation[3] Detection → Eluent Elutions ↓	Distillation Temp. & Pressure[4] or mp
[93] (151)	CH_2=$CHNO_2$ trans-B	76	3.3	3.0	$CHCl_3$, 60° 3.0 hrs.	(25, 3) uv (18, 2) uv	100°, 0.7 mm
[93] (157)	CH_2=$CHSO_2Ph$	86	2.5	2.5	$CHCl_3$, 80° 13.0 hrs.	(25, 4) uv	
	(Cis-trans mixture)-A	32				(25, 6) uv	solid cis-trans mixture
	(only the trans-isomer isolated) trans-B	68				(25, 6) uv	mp 82.5 - 84.5
[93] [104] (158)	H-C≡C-C≡N C	82	3.1	3.3	C_6H_6, 50° 6.0 hrs.	(60, 2) uv (45, 2) uv	Decomposition at 65°, 0.8 mm

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, (158) refers to page 158.

2. All reactions were carried out in ~ 3 ml of solvent.

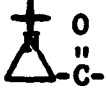
3. Separations were carried out on plc plates (EM Reagents Silica Gel-F254). The eluent was X% ethyl acetate in cyclohexane, v/v. Each set of data in parentheses for a given reaction refers to separation on a separate plc plate.

4. The final step in the purification of liquids was short-path distillation. The temperature of the oil bath and the distillation pressure are reported.

TABLE XXA

REACTIONS OF N-t-BUTYLNITRONE WITH ALKYNES: SYNTHESIS OF ISOXAZOLINES

A = 5-Substituted Isoxazolines; B = 4-Substituted Isozaxolines

Cross Ref.[1]	Product	Yield(%)	Nitrone (mmol)	Alkene (mmol)	Reaction Conditions[2]	Plc Separation[3] Detection → Eluent Elutions ↓	Distillation Temp. & Pressure or mp
[93] [104] (158) (160)	H-C≡C-C≡N (very exothermic reaction)	58	4.9	4.9	CCl_4, 25°, 5 min. (Mixed at 0°)	(50, 3) uv	
	A	50				(50, 3) uv	41°, 0.9 mm
	B	50				(50, 3) uv	52°, 0.8 mm
[93] [104] (158) (160)	H-C≡C-CO_2Et	71	2.6	3.2	CCl_4, 25°, 3 hrs.	(50, 2) uv	
	A	70				(35, 3) uv	54°, 1.0 mm
	B	30				(35, 3) uv	64°, 0.9 mm
[84] [104] (158)	H-C≡C-Ph	80	1.9	2.2	CCl_4, 75°, 3.5 hrs.	(25, 2) uv (25, 2) uv	78°, 1.0 mm
[81] [104] (158)	HC≡C-$(CH_2)_3$-Ph (A)* *isolated as:  -C-$(CH_2)_3$-Ph	36	3.2	6.0	CCl_4, 85° 5 hrs.	(20, 2) I_2 (20, 2) I_2	120°, 0.5 mm

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, (158) refers to page 158.

2. All reactions were carried out in ~ 3 ml. of solvent.

3. Separations were carried out on plc plates (EM Reagents Silica Gel-F254). The eluent was X% ethyl acetate in cyclohexane, v/v. Each set of data in parentheses for a given reaction refers to separation on a separate plc plate.

4. The final step in the purification of liquids was short-path distillation. The temperature of the oil bath and the distillation pressure are reported.

TABLE XVIIIB

REACTIONS OF N-t-BUTYLNITRONE WITH ALKENES: ANALYTICAL DATA FOR ISOXAZOLIDINES

A = 5-Substituted Isoxazolidines; B = 4-Substituted Isoxazolidines

Cross Ref.[1]	Product		Mass Spectral Data	Elemental Analysis
[87]	CH_2=$CHCO_2CH_3$	A	M^+, 187(13); 172(47); 131(31); 128(16); 101(25); 87(31); 72(76); 70(25); 59(25); 57(100); 56(31); 55(26); 44(33); 43(21); 42(35); 41(65).	$C_9H_{17}NO_3$ Calcd: C, 57.73; H, 9.17 Found: C, 57.76; H, 9.33
[87]	CH_2=CHC≡N	A	M^+, 154(13); 139(22); 98(30); 57(100); 56(45); 41(45).	$C_8H_{14}N_2O$ Calcd: C, 62.30; H, 9.17 Found: C, 62.20; H, 9.31
[87]	CH_2=$C(CH_3)CO_2CH_3$	A	M^+, 201(10); 186(38); 145(16); 87(100); 85(27); 59(19); 57(57); 56(23); 44(27); 43(79); 42(18); 41(45).	$C_{10}H_{19}NO_3$ Calcd: C, 59.67; H, 9.53 Found: C, 59.66; H, 9.65
[87]	CH_2=C(OAc)C≡N	A	M^+, 212(1); 155(5); 143(7); 128(8); 87(22(; 57(100); 43(30).	$C_{10}H_{16}N_2O_3$ Calcd: C, 56.58; H, 7.61 Found: C, 56.59; H, 7.69
[87]	CH_2=$C(CH_3)$C≡N	A	M^+, 168(15); 153(39); 112(59); 82(18); 68(34); 57(100); 56(41); 44(40); 41(61).	$C_9H_{16}N_2O$ Calcd: C, 64.24; H, 9.60 Found: C, 64.16; H, 9.40
[93]	CH_2=$CHSO_2Ph$	A	M^+, 269(7); 254(10); 128(59); 127(16); 126(19); 72(100); 77(31); 57(85).	$C_{13}H_{19}NO_3S$. Calcd: C, 57.96; H, 7.12; N, 5.20. Found: C, 57.80; H, 7.26; N, 5.12.
		B	Not isolated in pure form.	Data not obtained.

TABLE XVIIIB (Continued)

	$CH_3CH{=}CHCHO$ (trans)	A&B	Data not obtained.	Data not obtained
[84]	$CH_2{=}CHPh$	A	M^+, 205(26); 190(89); 172(20); 149(49); 132(17); 130(26); 118(42); 117(100); 115(32); 106(28); 105(100); 104(100); 103(26); 91(30); 84(17); 78(32); 77(96); 70(47); 58(28); 57(100); 56(38); 41(94).	$C_{13}H_{19}NO$ Calcd: C, 76.04; H, 9.35 Found: C, 75.95; H, 9.36
[81]	$CH_2{=}CH{-}S{-}Ph$	A	M^+, 237(43); 222(14); 149(61); 136(39); 135(32); 128(82); 125(29); 110(68); 109(39); 84(43); 77(36); 72(68); 66(39); 57(100); 41(79); 40(64).	$C_{13}H_{19}NOS$ Calcd: C, 65.77; H, 8.08 Found: C, 65.86; H, 8.23
[81]	$CH_2{=}CH{-}O{-}CH_2CH(CH_3)_2$	A	M^+, 201(34); 186(46); 145(14); 130(16); 128(55); 113(25); 89(64); 84(22); 61(25); 57(41); 56(25); 41(100).	$C_{11}H_{23}NO_2$ Calcd: C, 65.62; H, 11.54 Found: C, 65.60; H, 11.36
[87]	$CH_3CH{=}CHCO_2CH_3$ (trans)	A	M^+, 201(37); 187(23); 186(98); 145(88); 142(42); 115(31); 101(98); 86(98); 84(65); 70(88); 69(100); 58(98); 57(98); 56(98); 42(98); 41(98).	$C_{10}H_{19}NO_3$ Calcd: C, 59.67; H, 9.53 Found: C, 59.63; H, 9.57
		B	M^+, 201(43); 187(22); 186(100); 145(57); 114(16); 101(100); 70(98); 69(98); 57(98); 41(100).	$C_{10}H_{19}NO_3$ Calcd: C, 59.67; H, 9.53 Found: C, 59.69; H, 9.60
[81]	$CH_2{=}CH{-}O{-}Ac$	A	M^+, 187(3); 112(16); 84(24); 72(26); 70(60); 60(40); 57(100); 56(28); 55(16); 41(77).	$C_9H_{17}NO_3$ Calcd: C, 57.72; H, 9.17 Found: C, 57.74; H, 9.34

TABLE XVIIIB (Continued)

[87]	$PhCH{=}CHCO_2CH_3$ A,B (trans) (mixture)	M^+, 263(0.5); 162(8); 131(11); 103(8); 77(6); 57(34); 56(66); 55(26); 45(65); 41(100).	$C_{15}H_{21}NO_3$ Calcd: C, 68.40; H, 8.05 Found: C, 68.49; H, 8.10
[81]	$CH_2{=}CH(CH_2)_2$-Ph A	M^+, 233(11); 218(43); 104(48); 91(48); 57(48); 43(100); 41(41).	$C_{15}H_{23}NO$ Calcd: C, 77.21; H, 9.93 Found: C, 77.04; H, 9.95
[84]	$CH_2{=}C(CH_3)Ph$ A	M^+, 219(91); 205(21): 204(63); 163(50); 146(67); 132(54); 131(70); 119(24); 118(100); 117(70); 116(17); 115(22); 103(36); 102(32); 91(63); 77(50); 57(85); 46(65).	$C_{14}H_{21}NO$ Calcd: C, 76.65; H, 9.67 Found: C, 76.51; H, 9.74
[84]	$CH_3CH{=}CHPh$ A (trans)	M^+, 219(19); 204(56); 163(14); 131(36); 118(100); 117(28); 105(16); 91(15); 77(13); 57(43); 41(30).	$C_{14}H_{21}NO$ Calcd: C, 76.65; H, 9.67 Found: C, 75.98; H, 9.57

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, [84] refers to page 84.

TABLE XIXB

REACTIONS OF C-PHENYL-N-METHYLNITRONE WITH ALKENES AND ALKYNES: ANALYTICAL DATA

A = 5-Substituted Isoxazolidines; B = 4-Substituted Isoxazolidines; C = 4-Substituted Isoxazoline

Cross Ref.[1]	Product	Mass Spectral Data	Elemental Analysis
[93] (151)	CH_2=$CHNO_2$ trans-B	M^+, 208(11); 161(21); 160(34); 135(63); 134(88); 132(56); 131(81); 119(44); 118(75); 107(16); 103(63); 91(36); 77(100); 51(65).	$C_{10}H_{12}N_2O_3$ Calcd: C, 57.67; H, 5.82 Found: C, 57.93; H, 5.89
[93] (157)	CH_2=$CHSO_2Ph$ (cis-trans mixture)-A	M^+, 303(15); 163(13); 162(100); 161(30); 160(36); 134(79); 132(22); 125(30); 119(41); 118(31); 91(24); 77(69); 51(31); 42(21).	Analysis not obtained
	trans-B (only the trans-isomer isolated.)	M^+, 303(36); 162(12); 161(100); 160(97); 134(17); 118(27); 91(23); 77(33); 117(23).	$C_{16}H_{17}NO_3S$. Calcd: C, 63.34; H, 5.66; N, 4.62. Found: C, 63.09; H, 5.69; N, 4.50
[93] [104] (158)	H-C≡C-C≡N C	M^+, 186(4); 119(24); 118(39); 107(17); 106(97); 105(94); 91(12); 77(97); 57(42); 51(100).	$C_{11}H_{10}N_2O$ Calcd: C, 70.94; H, 5.42 Found: C, 70.64; H, 5.59

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, (158) refers to page 158.

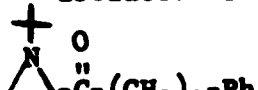
TABLE XXB

REACTIONS OF N-t-BUTYLNITRONE WITH ALKYNES: ANALYTICAL DATA FOR ISOXAZOLINES

A = 5-Substituted Isoxazolines; B = 4-Substituted Isoxazolines

Cross Ref.[1]	Product		Mass Spectral Data	Elemental Analysis
[93] [104] (158) (160)	H-C≡C-C≡N	A	M^+, 152(66); 137(43); 109(17); 96(66); 95(31); 83(15); 82(17); 70(17); 69(20); 68(100); 67(25); 58(45); 57(100); 56(28); 55(40); 54(24); 41(100).	$C_8H_{12}N_2O$ Calcd: C, 63.12; H, 7.96 Found: C, 62.82; H, 7.95
		B	M^+, 152(26); 137(12); 109(28); 96(100); 95(26); 82(18); 69(37); 68(40); 67(38); 58(34); 57(34); 56(18); 55(36); 43(26); 42(53); 41(86); 40(45); 39(21).	$C_8H_{12}N_2O$ Calcd: C, 63.12; H, 7.96 Found: C, 62.85; H, 8.04
[93] [104] (158) (160)	H-C≡C-CO_2Et	A	M^+, 199(10); 184(11); 143(41); 142(37); 70(23); 58(54); 57(100); 55(15); 54(19); 42(27); 41(43).	$C_{10}H_{17}NO_3$ Calcd: C, 60.28; H, 8.62 Found: C, 60.14; H, 8.61
		B	M^+, 199(12); 184(4); 143(34); 142(22); 115(15); 70(23); 69(25); 57(100); 56(23); 44(38); 41(60).	$C_{10}H_{17}NO_3$ Calcd: C, 60.28; H, 8.62 Found: C, 60.19; H, 8.60
[84] [104] (158)	H-C≡C-Ph	A	M^+, 203(7); 147(24); 146(40); 105(59); 77(44); 70(26); 58(18); 57(100); 56(26); 41(79).	$C_{13}H_{17}NO$ Calcd: C, 76.80; H, 8.45 Found: C, 76.67; H, 8.39

TABLE XXB (Continued)

[81] [104] (158)	H-C≡C-$(CH_2)_3$-Ph [A]* *Isolated as 	M^+, 245(6); 230(37); 154(35); 141(35); 104(51); 98(40); 91(56); 85(37); 84(23); 70(30); 57(100); 44(23); 42(30); 41(47).	$C_{16}H_{23}NO$ Calcd: C, 78.31; H, 9.47 Found: C, 78.14; H, 9.30

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, (158) refers to page 158.

TABLE XVIIIC

REACTIONS OF N-t-BUTYLNITRONE WITH ALKENES: ANALYTICAL DATA FOR ISOXAZOLIDINES

A = 5-Substituted Isoxazolidines; B = 4-Substituted Isoxazolidines

Cross Ref.[1]	Product		UV Spectrum λ_{max}^{MeOH} nm(ε) N = No λ_{max} above 210 nm	IR Spectrum λ(microns) s = strong; m = medium; w = weak; b = broad	NMR Spectrum
[87]	CH_2=$CHCO_2CH_3$	A	290(13.9)	(film): (C=O), 5.74(s); 6.98(s); 7.35(s); 8.30(b); 9.25(b).	(CCl_4): δ 4.30(-OC$\underline{H}$$CO_2CH_3$, dd, J=6.2, 6.2 Hz, 1H); 3.67(-OCH_3, s, 3H); 3.20-2.00(-CH_2CH_2-, m, 4H); 1.08(t-butyl, s, 9H). Nmr Spectrum No. 42.
[87]	CH_2=CHC≡N	A	N	(film): (C≡N), 4.5(w); 7.36(s); 8.17(s); 9.62(s).	(CCl_4): δ 4.80-4.40(-OCHCN, m, 1H); 3.30-2.10(-CH_2CH_2-, m, 4H); 1.10(t-butyl, s, 9H).
[87]	CH_2=C(CH_3)CO_2CH_3	A	290(13.7)	(film): (C=O), 5.77(s); 6.91(b); 7.38(s); 7.77(b); 8.30(b); 8.82(b).	(CCl_4); δ 3.64(-OCH_3, s, 3H); 3.00-1.50 (-CH_2CH_2-, m, 4H); 1.38(-C($\underline{CH_3}$)CO_2CH_3, s, 3H); 1.04(t-butyl, s, 9H).
[87]	CH_3=C(OAc)C≡N	A	N	(film): (C=O), 5.69(s); 7.34(s); 8.14(b); 8.89(s); 9.52(b); 9.90(s); 10.41(s).	(CCl_4) δ 3.30-2.30(-CH_2CH_2-, bm, 4H); 2.10(-$OCOCH_3$, s, 3H); 1.11(t-butyl, s, 9H).

TABLE XVIIIC (Continued)

[87]	CH_2=C(CH_3)C≡N	A	N	(film): (C≡N), 4.50(w); 6.94(s); 7.39(s); 8.16(s); 8.84(b); 10.86(s)	(CCl_4): δ 3.40-1.80(-CH_2CH_2-, m, 4H); 1.60(-CH_3, s, 3H); 1.10(t-butyl, s, 9H)
[93]	CH_2=$CHSO_2Ph$	A	266(1,160); 218(9,630)	(CCl_4): (SO_2), 7.55(s), 8.62(s); 6.90(m); 9.35(s); 13.80(w); 14.54(s)	($CDCl_3$): δ 8.15-7.25(Ar-H, m, 5H); 3.20-2.40(-CH_2CH_2-, bm, 4H); 1.05(t-butyl, s, 9H); 5.10-4.70(-$CHSO_2Ph$, m, 1H) Nmr Spectrum No. 53
		B	Product not obtained in pure form		($CDCl_3$): δ 8.15-7.25(Ar-H, m, 5H); 4.40-3.80(-OCH_2CHSO_2Ph, m, 3H); 3.40-3.00 (-CH_2N-, m, 2H); 1.05(t-butyl, s, 9H) Nmr Spectrum No. 54
[87]	CH_3CH=CHCHO (trans)	A	Uv spectrum not recorded		(CCl_4): δ 9.50(-CHO, d, J=1.5 Hz, 1H); 3.56(-OCHCHO, dd, J=1.5, 4.0 Hz, 1H); 3.28-1.28(ring-H, m, 3H); 1.22(-CH_3, d, J=7.0 Hz, 3H); 1.08(t-butyl, s, 9H)
		B	Uv spectrum not recorded		(CCl_4): δ 9.62(-CHO, d, J=3.0Hz, 1H); 4.45-3.75(-NOCH-, 5 line A_3BX pattern, 1H); 3.35-1.85(ring-H, m, 3H); 1.33 (-CH_3, d, J=7.0 Hz, 3H); 1.08(t-butyl, s, 9H)
[84]	CH_2=CHPh	A	258(210)	(film): 6.28(w); 6.75(s); 6.83(s); 6.94(s); 7.28(s); 7.39(s); 8.16(b); 9.64(b); 13.25(b); 14.34(b).	(CCl_4): δ 7.20(Ar-H, s, 5H); 4.86(-OCHPh, dd, J=7.0,7.0 Hz, 1H); 3.10-1.50(-CH_2CH_2-, m, 4H); 1.12(t-butyl, s, 9H)

TABLE XVIIIC (Continued

[81]	CH_2=CH-S-Ph	A	249(7,090)	(film): 6.30(m); 6.78(s); 7.35(s); 8.13(s); 9.40(m); 12.25(w); 13.37(b); 14.45(b)	(CCl_4): δ 7.60-7.00(Ar-H, m, 5H); 5.50-5.10(-OCHSPh, m, 1H); 3.10-1.70(-CH_2CH_2-, m, 4H); 1.12(t-butyl, s, 9H)
[81]	CH_2=CH-O-CH_2-$CH(CH_3)_2$	A	N	(film): 6.86(m); 7.40(s); 9.19(b); 9.74(s); 9.89(s); 10.14(s)	(CCl_4): δ 4.86(-OCHO-, dd, J=3.0, 4.5 Hz, 1H); 3.60-1.40(-CH_2CH_2- and -OCH_2CH-, m, 7H); 1.04(t-butyl, s, 9H); 0.90 (-CH($\underline{CH_3}$)$_2$, d, J=7.5 Hz, 6H)
[87]	CH_3CH=$CHCO_2CH_3$ (trans)	A	285(44.9)	(CCl_4): (C=O), 5.60(s); 5.67(s); 5.76(s); 7.35(s); 7.85(b); 8.35(b); 9.78(s)	($CDCl_3$): δ 3.98(-O$\underline{CH}CO_2CH_3$, d, J=6.0 Hz, 1H); 3.73(-OCH_3, s, 3H); 3.40-1.90 (ring-H, m, 3H); 1.50-1.00(-CH$\underline{CH_3}$ and t-butyl, m, 12H) Figure 18, page 91.
		B	285(9.40)	(film): (C=O), 5.78(s); 7.00(s); 7.38(s); 11.03(b); 12.10(m)	(CCl_4): δ 4.30-3.80(-O$\underline{CH}(CH_3)$-, 5 line A_3MX pattern, 1H); 3.67(-OCH_3, s, 3H); 3.30-2.40(ring-H, m, 3H); 1.28(-CH$\underline{CH_3}$, d, J=6.0 Hz, 3H); 1.04(t-butyl, s, 9H) Figure 19, page 92.
[81]	CH_2=CH-O-Ac	A	N	(film): (C=O), 5.75(s); 7.37(s); 8.10(b); 10.19(b)	(CCl_4): δ 6.30-6.00(-OCHOAc, m, 1H); 3.20-2.10(-CH_2CH_2-, m, 4H); 1.98(-$OCOCH_3$, s, 3H); 1.07(t-butyl, s, 9H).
[87]	PhCH=$CHCO_2CH_3$ (trans)	A&B	258(303)	(film): (C=O), 5.76(s); 6.25(w); 13.14(b); 14.30(b)	($CDCl_3$): δ 7.52-7.10(Ar-H, m, 5H); 5.30-5.00(PhCH-, m, 9/13H); 4.55-4.10 (-$CHCO_2CH_3$, m, 4/13H); 3.72(-OCH_3, s, 3H); 3.62-2.50(ring-H, bm, 3H); 1.18 (t-butyl, s, 9H). Nmr Spectrum No. 45.

TABLE XVIIIC (Continued)

[81]	CH_2=CH(CH_2)$_2$-Ph	A	250(164)	(film): 6.27(w); 6.74(m); 6.84(m); 6.94(s); 7.41(s); 8.15(s); 13.43(b); 14.33(b)	(CCl_4): δ 7.08(Ar-H, s, 5H); 4.10- 3.55 (-CH_2C<u>H</u>CH_2, 5 line $A_2BB'X$ pattern, 1H); 2.90-2.35(-CH_2-, bm, 4H); 2.35-1.30(-CH_2-, bm, 4H); 1.05(t-butyl, s, 9H)
[84]	CH_2=C(CH_3)-Ph	A	258(230)	(film): 6.24(w); 6.94(s); 7.40(s); 8.11(s); 13.10(b); 14.30(b)	(CCl_4): δ 7.50-6.90(Ar-H, m, 5H); 3.10-1.90(-CH_2CH_2-, m, 4H); 1.48(-CH_3, s, 3H); 1.13(t-butyl, s, 9H)
[84]	CH_3CH=CHPh (trans)	A	258(451)	(film): 6.24(w); 6.92(s); 7.37(s); 8.17(s); 9.82(b); 13.28(b); 14.32(b)	(CCl_4): δ 7.22(Ar-H, s, 5H); 4.28 (-OCHPh, d, J=7.2 Hz, 1H); 3.35-2.80 (ring-H, m, 1H); 2.80-1.90(ring-H, m, 2H); 1.14(-CH_3, d, J=4.0 Hz, 3H); 1.12 (t-butyl, s, 9H)

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, [84] refers to <u>page</u> 84.

TABLE XIXC

REACTIONS OF C-PHENYL-N-METHYLNITRONE WITH ALKENES AND ALKYNES: ANALYTICAL DATA

A = 5-Substituted Isoxazolidines; B = 4-Substituted Isoxazolidines; C = 4-Substituted Isoxazoline

Cross Ref.[1]	Product	UV Spectrum λ_{max}^{MeOH} nm (ε) N = No λ_{max} above 210 nm	IR Spectrum λ (microns) s = strong; m = medium; w = weak; b = broad	NMR Spectrum
[93] (151)	CH_2=$CHNO_2$ trans-B	285(656)	(film): (NO_2), 6.41(s), 7.29(s); 9.59(s); 11.52(m); 12.09(m); 13.12(b); 14.27(b)	(CCl_4): δ 7.30(Ar-H, s, 5H); 4.95(-$CHNO_2$, ddd, J=3.0, 6.0, 6.7 Hz, 1H); [ABX octet: 4.44(-$OCHCNO_2$-cis, dd, J=3.0, 10.5 Hz, 1H); 4.15(-$OCHCNO_2$-trans, dd, J=6.7, 10.5 Hz, 1H)]; 3.95(-CHPh-, d, J=6.0 Hz, 1H); 2.57(NCH_3, s, 3H)
	cis-B	Not isolated		($CDCl_3$): δ 7.26(Ar-H, s, 5H); 5.46 (-$CHNO_2$, ddd, J-5.5, 8.0, 8.0 Hz, 1H); [ABX octet: δ 4.62(-$OCHCNO_2$-cis, dd, J= 5.5, 10.5 Hz, 1H); 4.34(-$OCHCNO_2$-trans, dd, J=8.0, 10.5 Hz, 1H)]; 3.87(-CHPh, d, J=8.0 Hz, 1H); 2.61(-NCH_3, s, 3H)
[93] (157)	CH_2=$CHSO_2Ph$ A (cis and trans mixture)	Spectrum not recorded	(CCl_4): (SO_2), 7.55(s), 8.66(s); 6.90(m); 9.40(s); 10.97(s); 13.80(m); 14.32(s); 14.57(s)	($CDCl_3$): δ 8.20-7.10(Ar-H, m, 10H); 5.02(-$OCHSO_2Ph$, dd, J=3.0, 8.3 Hz, 1H); 3.95(NCHPh, dd, J=6.0, 10.0 Hz, 1H); 3.70-2.50(-CH_2-, m, 2H); 2.70 and 2.49 (N-CH_3 of cis and trans isomers, s, 3H)

TABLE XIXC (Continued)

[93] (157)	CH_3-CHSO_2Ph trans-B (only the trans isomer isolated)	265(1,070)	(CCl_4): (SO_2), 7.58(s), 8.67(s); (C=O), 9.21(m); 6.98(w); 14.36(m); 14.57(m)	($CDCl_3$): δ 7.95-7.20(Ar-H, m, 5H); 7.18 (Ar-H, s, 5H); 4.70-3.60(ring-H, m, 4H); 2.58(NCH_3, s, 3H) Nmr Spectrum No. 59.
[93] [104] (158)	H-C≡C-C≡N C	251(5,140)	(film); (C≡N), 4.50(s); (C=C), 6.18(s); 6.92(s); 8.72(s); 9.04(b); 13.07(b); 13.38(b); 14.33(b)	(CCl_4): δ 7.30(Ar-H, s, 5H); 7.10(vinyl-H, d, J=2.0 Hz, 1H); 4.78(PhCH-, d, J= 2.0 Hz, 1H); 2.85(-NCH_3, s, 3H)

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, (158) refers to page 158.

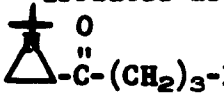
TABLE XXC

REACTIONS OF N-t-BUTYLNITRONE WITH ALKYNES: ANALYTICAL DATA FOR ISOXAZOLINES

A = 5-Substituted Isoxazoline; B = 4-Substituted Isoxazolines

Cross Ref.[1]	Product		UV Spectrum λ_{max}^{MeOH} nm (ε) N = No λ_{max} above 210 nm	IR Spectrum λ (microns) s = strong; m = medium; w = weak; b = broad	NMR Spectrum
[93] [104] (158) (160)	H-C≡C-C≡N	A	265(1,690)	(film): (C≡N), 4.50(m); (C=C), 6.12(s); 6.81(s); 7.37(s); 7.92(s); 8.12(s); 8.50(b); 10.37(b); 12.47(m); 13.32(b)	(CCl_4): δ 5.62(vinyl-H, t, J-3.0 Hz, 1H); 4.05(-CH_2-, d, J=3.0 Hz, 2H); 1.10(t-butyl, s, 9H) Nmr Spectrum No. 51a.
		B	265(4,690)	(film): (C≡N), 4.50(s); (C=C), 6.20(s); 6.86(s); 7.40(s); 8.30(s); 8.84(b); 13.74(b)	(CCl_4): δ 7.10(vinyl-H, t, J=2.0 Hz, 1H); 4.05(-CH_2-, d, J-2.0 Hz, 2H); 1.10(t-butyl, s, 9H) Nmr Spectrum No. 52a.
[93] [104] (158) (160)	H-C≡C-CO_2Et	A	277(2,060)	(film): (C=O), 5.78(s); (C=C), 6.09(s); 7.35(s); 7.53(s); 7.85(s); 8.00(s); 8.24(s); 8.85(b); 9.82(s)	(CCl_4): δ 5.60(vinyl-H, t, J=2.5 Hz, 1H); 4.00(NCH_2-, d, J=2.5 Hz, 2H); 1.10(t-butyl, s, 9H); [A_3X_2 pattern of -CH_2CH_3: 4.20(-CH_2-, q, J=7.3 Hz, 2H); 1.33(-CH_3, t, J=7.3 Hz, 3H)]

TABLE XXC (Continued)

[93] [104] (158) (160)	$H-C\equiv C-CO_2C_2H_5$	B	275(6,200)	(film): (C=O), 5.83(s); (C=C), 6.08(s); 8.75(b); 9.00(b); 13.21(m)	(CCl_4): δ 7.11(vinyl-H, t, J-2.0 Hz, 1H); 3.98(NCH_2-, d, J=2.0 Hz, 2H); 1.10(t-butyl, s, 9H); [A_3X_2 pattern of $-CH_2CH_3$: 4.10($-CH_2$-, q, J=7.3 Hz, 2H); 1.27($-CH_3$, t, J=7.3 Hz, 3H)]
[84] [104] (158)	H-C≡C-Ph	A	282(3,720) 226(9,160)	(film): 5.92(w); 6.03(m); 6.15(s) 7.36(s); 8.15(s); 9.48(s); 9.77(s); 12.95(b); 14.15(b)	(CCl_4): δ 7.63-7.03(Ar-H, m, 5H); 5.00 (vinyl-H, t, J=2.5 Hz, 1H); 4.00($-CH_2$-, J=2.5 Hz, 2H); 1.12(t-butyl, s, 9H)
[81] [104] (158)	$H-C\equiv C-(CH_2)_3-Ph$  *Isolated as $-C-(CH_2)_3-Ph$	[A]*	258(295)	(film): (C=O) 5.85(s); 6.68(m); 6.86(m); 7.31(s); 8.12(s); 13.30(b); 14.26(b)	(CCl_4): δ 7.10(Ar-H, s, 5H); 2.80-1.50 ($-CH_2$-, bm, 9H); 0.94(t-butyl, s, 9H)

1. Numbers in parentheses refer to related data in Section III, Part C. Numbers in brackets refer to related discussions in Section II, Part B. For example, (158) refers to page 158.

a. Reaction of Nitroethylene and N-t-Butylnitrone: Synthesis of 2-t-Butyl-5-Nitroisoxazolidine

A 0.23 g (3.1 mmol) quantity of nitroethylene and 1.61 g (3.4 mmol) of N-t-butylnitrone solution (CCl_4, 2.1 mmol/g sol'n) were mixed in a test tube at 0° C, sealed under nitrogen, and allowed to slowly warm up to room temperature. After 5 minutes at room temperature, tlc (75%, 1 elution) revealed one major spot (Iodine development), R_f = 0.50. The reaction mixture was placed on a 20 x 40 cm silica gel plc plate and eluted twice with 50% ethyl acetate in cyclohexane. The product totally decomposed on the plc plate and no recognizable compounds could be isolated. Likewise, an aluminum oxide plc plate could not be used. The product was stable in the reaction solvent under nitrogen for several days. Nmr spectrum (CCl_4): δ 5.60-5.40 ($-OCHNO_2$, m, 1H); 3.20-2.60 ($-CH_2CH_2-$, bm, 4H); 1.13 (t-butyl, s, 9H).

b. Reaction of Nitroethylene and C-Phenyl-N-Methylnitrone: Synthesis of cis- and trans-2-Methyl-3-Phenyl-4-Nitroisoxazolidine

Data for this reaction and the products are given in Tables XIXA-XIXC. Only the trans product could be isolated. Tlc (25%, 1 elution) of the reaction mixture contained two spots (uv and iodine detection), R_f = 0.25, 0.35. Preparative layer chromatography (silica gel) was accompanied by total isomerization (presumably due to the silica gel) to the more stable trans-product which was isolated and characterized. Isomerization (monitored by nmr spectroscopy) was also effected by shaking the reaction mixture in deuterochloroform with an aqueous potassium hydroxide solution.

The percentage of the cis isomer in a reaction mixture was determined by nmr spectroscopy to be 74%. Nmr spectrum of cis-2-methyl-3-phenyl-4-nitroisoxazolidine in $CDCl_3$: δ 7.26 (Ar-H, s, 5H); 5.46 ($-CHNO_2$, ddd, J = 5.5, 8.0, 8.0 Hz, 1H); [ABX octet: δ 4.62 ($-OCHCNO_2$-cis, dd, J = 5.5, 10.5 Hz, 1H); 4.34 ($-OCHCNO_2$-trans, dd, J = 8.0, 10.5 Hz, 1H)]; 3.87 (-CHPh, d, J = 8.0 Hz, 1H); 2.61 ($-NCH_3$, s, 3H).

c. Reaction of 1-N-Morpholino-1-Cyclohexene and N-t-Butylnitrone

A 0.51 g (3.0 mmol) quantity of enamine and 1.51 g (3.2 mmol) of N-t-butylnitrone solution (CCl_4, 2.1 mmol/g sol'n) were mixed at room temperature and the solution was heated in a sealed tube under nitrogen for 6 hrs. at 70°. The reaction mixture was placed on a plc plate and eluted twice with ethyl acetate. A 2.5 cm strip of the plc plate was exposed for 30 minutes in an iodine developing tank. The major fraction (excluding the iodine stained portion) was scraped from the plate and extracted with ethyl acetate (~ 200 ml). The solvent was removed at reduced pressure to afford 332 mg of a white solid which was crystallized from methylene chloride, mp 108-111° C. The nmr spectrum of the isolated solid vaguely resembles the nmr spectrum of the reaction mixture. Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.04; H, 10.83; N, 6.95. Ms: M^+, 199(16); 184(26); 124(14); 111(76); 102(20); 98(38); 83(24); 74(40); 70(32); 67(44); 57(100); 41(92). Ir: Spectrum No. 40. Nmr ($CDCl_3$): Spectrum No. 40.

A definite structure for this compound has not been assigned. Other workers have reported "unpredictable" products from the reactions of nitrones and enamines.[34]

d. Reaction of Phenyl Isocyanate and N-t-Butylnitrone: Synthesis of 2-t-Butyl-4-Phenyl-1,2,4-Oxadiazolidin-5-one

A 0.37 g (3.1 mmol) quantity of phenyl isocyanate and 2.38 g (3.2 mmol) of N-t-butylnitrone (CCl_4, 1.3 mmol/g sol'n) were mixed at room temperature and heated at 50° in a sealed tube under nitrogen for 1 hr. Tlc of the reaction mixture had only one spot (uv detection). The product was isolated by plc [(50%, 1 elution), uv detection] in 82% yield. Crystallization from benzene-petroleum ether (30-60°) gave white crystals, mp 102-104°. Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.42; H, 7.34; N, 12.72. Found: C, 65.64; H, 7.47; N, 12.78. Ms: M^+, 220(72); 176(23); 164(100); 149(25); 120(38); 119(23); 105(24); 104(24); 93(46); 77(38); 70(31); 57(49). Ir (CCl_4): (C=O), 5.68 μ, (s); (C-N), 7.12, (s); 6.26, (m): 14.54, (m); 14.87, (m). Uv (MeOH); λ_{max} 236 nm, (ε 17,600). Nmr ($CDCl_3$): δ 7.60-6.90 (Ar-H, m, 5H); 4.95 ($-CH_2-$, s, 2H); 1.20 (t-butyl, s, 9H).

A deuterochloroform solution of the compound in an nmr tube was shaken periodically for an hour with a solution of anhydrous Na_2CO_3 in D_2O. No change in the nmr spectrum was observed. Consequently, the product is the 1,2,4-oxadiazolidin-5-one and not the 1,2,5-oxadiazolidin-4-one.

e. Reaction of Cyanoacetylene and C,N-Diphenylnitrone

A solution of 96.8 mg (0.49 mmol) of C,N-diphenylnitrone in 1.0 g of $CDCl_3$ was added to a solution of 36.8 mg (0.72 mmol) of cyanoacetylene in 0.50 g of $CDCl_3$ in an nmr tube. The reaction was completed after 3.5 hrs. at room temperature. The nmr spectrum of the reaction mixture had a singlet at δ 9.96, a doublet at δ 9.25, and several small

peaks between δ 6.50 and δ 3.00. Tlc of the reaction mixture (50%, 1 elution) had several spots (uv and iodine detection) between R_f = 0.20 and 0.60.

Apparently the 4-substituted Δ^4- isoxazoline initially formed in the reaction was undergoing rearrangement to an aziridine which was subsequently rearranging to a Δ^4-oxazoline.[46] Rearrangements of Δ^4-isoxazolines are discussed in Section II B. Products of the reaction were not isolated.

f. Attempted Reaction of Isopropenyl Acetate and N-t-Butylnitrone

A 75 mg (0.75 mmol) quantity of isopropenyl acetate and 0.56 g (0.75 mmol) of N-t-butylnitrone solution (CCl_4, 1.3 mmol/g sol'n) were dissolved in 1.0 g of CCl_4 in an nmr tube which was then purged with dry nitrogen and sealed with a flame. The reaction tube was heated in an oil bath for a given length of time, removed and rinsed with acetone to remove the oil, and the nmr spectrum was recorded. The results are summarized in the table below.

Time	Temp.	Peak Height of Methylene Proton Singlet of N-t-Butylnitrone	Peak Height of Vinyl Methyl Proton Singlet of Isopropenyl Acetate
	25°	X	Y
1 hr	70°	X	Y
1 hr	80°	X	Y
1 hr	90°	X	Y
1 hr	110°	½ X	Y
1hr	120°	1/10X	Y

The nitrone was apparently decomposing or dimerizing. A similar reaction mixture was heated at 100° C for five hours. The

N-t-butylnitrone slowly disappeared from the reaction mixture, while the isopropenyl acetate remained unchanged.

g. Attempted Reaction of Ethoxyacetylene and N-t-Butylnitrone

Optimum reaction conditions were determined by following a small scale reaction of 51 mg (0.73 mmol) of ethoxyacetylene [Nmr (CCl_4): δ 4.05 ($-CH_2-$, q, J = 7.5 Hz, 2H); 1.38 ($-CH_3$, t, J = 7.5 Hz, 3H); 1.34 (acetylenic −H, s, 1H)] and 0.61 g (0.78 mmol; CCl_4, 1.3 mmol/g sol'n) of N-t-butylnitrone solution in 1.0 g of carbon tetrachloride by nmr spectroscopy. After 2 hrs. at 50° in a sealed tube under nitrogen, the methylene proton singlet of N-t-butylnitrone at δ 6.30 had disappeared. The most distinguishing features of the nmr spectrum of the reaction mixture was a broad and weak multiplet at δ 4.60, a singlet at δ 1.98, a doublet at δ 1.72, and a broad intense multiplet at δ 0.90-1.65. A tlc (50%, 1 elution) of the reaction mixture had two major spots (iodine development).

A 0.24 g (3.4 mmol) quantity of ethoxyacetylene and 3.38 g (4.3 mmol) of N-t-butylnitrone solution (CCl_4, 1.3 mmol/g sol'n) were heated in a sealed tube under nitrogen at 50° for 2 hrs. Five fractions were isolated by plc [(50%, 1 elution), iodine detection, product extraction from silica gel with diethyl ether]. The nmr spectra of these fractions revealed that the reaction product(s) had decomposed on the plc plate.

h. Attempted Reaction of Vinylidene Cyanide and N-t-Butylnitrone

A 0.95 g (1.2 mmol) quantity of N-t-butylnitrone solution (CCl_4, 1.3 mmol/g sol'n) was filtered through a two-inch column of

anhydrous $MgSO_4$ and collected in a flame dried nmr tube. Vinylidene cyanide (0.10 g, 1.3 mmol) dissolved in 2 ml of CCl_4 dried over P_2O_5 was added dropwise with a flame dried pipet to the N-t-butylnitrone solution. The reaction was rapid and very exothermic. A white gel which was formed immediately slowly developed a red-orange color even when stored under dry nitrogen.

Numerous attempts to carry out this cycloaddition were without success. The N-t-butylnitrone solution was also dried over anhydrous $CaCl_2$ to remove any t-butylamine present. Again, polymeric material was formed. A carbon tetrachloride solution of N-t-butylnitrone free of t-butylamine and t-butylhydroxylamine contamination was specifically prepared for this reaction (Section III B) to no avail. Dilute solutions of vinylidene cyanide were added dropwise under argon to a dilute stirred solution of N-t-butylnitrone and vice-versa. Polymeric material was always formed.[63]

1. Attempted Reaction of Vinylidene Cyanide and C-Phenyl-N-Methylnitrone

Efforts to react C-phenyl-N-methylnitrone with vinylidene cyanide in benzene were totally unsuccessful. The C-phenyl-N-methylnitrone was crystallized from benzene-petroleum ether and sublimed at 70° and 0.5 mm. As with the attempted N-t-butylnitrone reactions, polymeric material was always formed.[63]

2. Related Reactions

a. Attempted Deuteration of 2-Methyl-3-Phenyl-5-Benzenesulfonyl-isoxazolidine

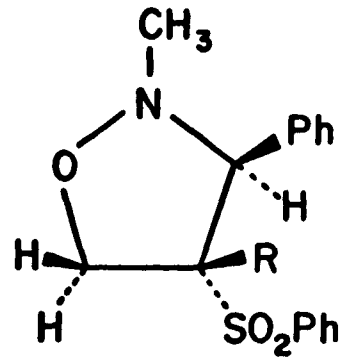
To a solution of 10 mg of EtONa in 3 ml of EtOD was added 155 mg of the isoxazolidine. The mixture was stirred under nitrogen at room temperature for 9 days. A few drops of D_2O were added to the basic solution and the mixture was placed on a layer of anhydrous Na_2SO_4 supported on a fritted glass filter. The isoxazolidine was flushed through the filter with chloroform at reduced pressure. The solvent was removed at reduced pressure, the residue was dissolved in deuterochloroform, and an nmr spectrum was recorded. No deuterium exchange had occurred. (See Tables XIXA-XIXC for preparation and characterization data for 2-methyl-3-phenyl-5-benzene-sulfonylisoxazolidine).

Similarly, the isoxazolidine did not undergo deuterium exchange in EtOD/KOH at 80° after 18 hrs.

b. Deuteration of trans-2-Methyl-3-Phenyl-4-Benzenesulfonyl-isoxazolidine

To 150 mg of the isoxazolidine in 1 ml of $CDCl_3$ was added 3 ml of a dilute D_2O/KOH solution. A few drops of dry THF were added and the mixture was stirred at room temperature for 18 hrs. under nitrogen. Subsequently, the mixture was placed on a layer of anhydrous Na_2SO_4 supported on a fritted glass filter. The isoxazolidine was flushed through the filter with chloroform at reduced pressure. The solvent was removed at reduced pressure, the residue was dissolved in deuterochloroform, and an nmr spectrum was recorded. Total deuterium

exchange had occurred. (See Tables XIXA-XIXC for preparation and characterization data for trans-2-methyl-3-phenyl-4-benzenesulfonylisoxazolidine).



I: R=H
II: R=D

Mass Spectra:

I	II
M^+, 303(36)	M^+, 304(24
162(12)	162(77)
161(100)	161(100)
160(97)	160(29)

Nmr Spectra:

I	II
δ 4.70-3.60 (ring-H, complex multiplet, 4H). Nmr Spectrum No. 59.	AB quartet: δ_B4.47, δ_A4.25 ($=CH_2-$, q, J=9.5 Hz, 2H), 3.87(-CHPh, s, 1H). Nmr Spectrum No. 59.

c. Rearrangement of 4-Substituted -Δ^4-Isoxazolines

Baldwin et al.,[48] have reported rearrangements of Δ^4-isoxazolines to aziridines followed by subsequent rearrangements to Δ^4-oxazolines. The rearrangements reported here were monitored by nmr spectroscopy and the products were not isolated. Under identical conditions, the nmr spectrum of the corresponding 5-substituted-Δ^4-isoxazolines remained unchanged. Preparation and characterization data for

the 4- and 5-substituted-Δ^4-isoxazolines are given in Tables XIXA-XIXC and XXA-XXC.

(1) Rearrangement of 2-t-Butyl-4-Cyano-Δ^4-Isoxazoline

A sample of the isoxazoline in carbon tetrachloride was heated in an nmr tube under nitrogen at 80°. After 4.5 hrs., the methylene doublet of the isoxazoline at δ 4.05 had completely disappeared. The nmr spectrum of the rearrangement product(s) had singlets at δ 9.25 and δ 6.52, a doublet at δ 3.35, and a complex multiplet at δ 1.60-1.10. Tlc (75%, 1 elution) had only one major spot (iodine development), R_f = 0.60.

(2) Rearrangement of 2-t-Butyl-4-Carboethoxy-Δ^4-Isoxazoline

A sample of the isoxazoline in carbon tetrachloride was heated in an nmr tube under nitrogen at 80°. After 16 hrs. the vinyl proton triplet of the isoxazoline at δ 7.10 had almost disappeared. The nmr spectrum of the rearrangement product(s) had broad and complex multiplets centered at δ 4.15 and δ 1.28 and broad singlets at δ 9.9, 6.67, 3.37, and 3.05. Tlc (20%, 1 elution) had one major and two minor spots (iodine development), R_f = 0.20, 0.33 (major), and 0.50.

(3) Rearrangement of 2-Methyl-3-Phenyl-4-Cyano-Δ^4-Isoxazoline

A sample of the isoxazoline in carbon tetrachloride was heated in an nmr tube under nitrogen at 85°. After 7.5 hrs., the methine proton doublet of the isoxazoline at δ 4.78 had disappeared. The nmr spectrum of the rearrangement product(s) had a singlet at δ 9.92, and complex multiplets centered at δ 7.50 and δ 2.80. Tlc (50%, 1 elution) had one major and two minor spots (uv detection), R_f = 0.07, 0.30, and 0.47 (major).

d. Solvent Effect Studies

2,4,6-Trimethylbenzonitrile oxide reacts with methyl propiolate to give a mixture of the regioisomeric isoxazoles, the ratio of which is solvent dependent. Huisgen has found that the ratio of 4- to 5-substituted isoxazoles formed in cyclohexane is 75:25, and that the ratio is 56:44 in methanol.[66] A similar solvent dependency for the formation of 4- and 5-substituted isoxazolines in the reaction of N-t-butylnitrone with cyanoacetylene and ethyl propiolate was investigated. Product ratios of reaction mixtures were measured by nmr spectroscopy.

(1) Reaction of Ethyl Propiolate and N-t-Butylnitrone in Methanol-d_4

The acetylenic proton of ethyl propiolate slowly undergoes deuterium exchange with CD_3OD at 25° (60% exchange in 1.5 hr.) However, the cycloaddition reaction was rapid and the deuterated solvent could be used.

A 77 mg (0.76 mmol) quantity of N-t-butylnitrone was dissolved in 0.25 g of CD_3OD and a 79 mg (0.81 mmol) quantity of ethyl propiolate was dissolved in 0.25 g of CD_3OD. The two solutions were mixed and left standing at room temperature in an nmr tube under nitrogen for 1 hour. Integration of the vinyl proton absorptions at δ 8.0 (2-t-butyl-4-carboethoxy-Δ^4-isoxazoline) and δ 7.3 (2-t-butyl-5-carboethoxy-Δ^4-isoxazoline) gave a ratio of 1:1.7 for the two adducts, respectively. A similar reaction in CCl_4 gave a corresponding ratio of 1:1.6.

(2) Reaction of Cyanoacetylene and N-t-Butylnitrone in Methanol

Cyanoacetylene was instantly deuterated in CD_3OD; consequently, the deuterated solvent could not be used.

A 79 mg (0.78 mmol) quantity of N-t-butylnitrone was dissolved in 0.50 g of CH_3OH and 43 mg (0.84 mmol) of cyanoacetylene was added dropwise. The mixture was left standing in a sealed tube under nitrogen at room temperature for 1 hr. The methanol was removed at reduced pressure, the residue was dissolved in CCl_4, and the nmr spectrum was recorded. Integration of the vinyl proton resonances at δ 7.10 (2-t-butyl-4-cyano-Δ^4-isoxazoline) and δ 5.62 (2-t-butyl-5-cyano-Δ^4-isoxazoline) gave a 1:1 ratio. Changing solvents introduced some impurities which reduced the accuracy of interpreting the integrations. An identical reaction gave the same results. A similar reaction in CCl_4 gave a corresponding product ratio of 1.1:1.

PART D Cycloadditions with Fulvenes

No reactions of nitrones and fulvenes have been reported in the literature.

Products for these reactions were isolated as described in Part C.

1. Reaction of 6,6-Dimethylfulvene and N-t-Butylnitrone

A 0.28 g (2.6 mmol) quantity of 6,6-dimethylfulvene was added to 2.25 g (2.9 mmol) of N-t-butylnitrone solution (CCl_4, 1.3 mmol/g sol'n) and the mixture was heated under nitrogen for 1 hr. at 70°. Five fractions were isolated by plc (25%, 1 elution, uv and iodine detection). The two fastest moving fractions were less than 11 mg each and were discarded. The methyl proton absorptions in the nmr spectra of the remaining three fractions were at δ 1.6-1.8 ppm indicating that no addition had occurred across the exo double bond of the fulvene.

Anal.	Yield	Ms.	Nmr
Fraction 3	54%	M^+, 207(19); 121(15); 120(27); 119(74); 106(100); 105(42); 91(83); 79(17); 77(19); 65(15); 57(75); 41(64).	Spectrum No. 75
Fraction 4	7% (2:1 adduct)		No olefinic protons.
Fraction 5	14%	M^+, 308 (2:1 adduct)	No olefinic protons.

2. Reaction of 6,6-Diphenylfulvene and N-t-Butylnitrone

A 0.20 g (0.87 mmol) quantity of 6,6-diphenylfulvene was added to 0.74 g (0.96 mmol) of N-t-butylnitrone solution (CCl_4, 1.3 mmol/g sol'n) and the mixture was heated under nitrogen at 70° for 1 hr. Five

fractions were isolated by plc (25%, 1 elution). The fastest moving fraction was excess fulvene. One fraction of less than 10 mg was discarded.

Anal.	Yield	Ms.	Nmr
Fraction 2	67%	M^+, 331(18; 244(30); 243(55); 232(39); 231(91); 230(100); 229(70); 228(36); 215(32); 202(20); 149(38); 70(18); 57(39).	Spectrum No. 76
Fraction 3	14%	M^+, 331(3); 244(22); (243(6); 230(6); 229(6); 77(2); 51(31); 49(100); 47(12).	Spectrum No. 77.
Fraction 5	11% (2:1 adducts)	M^+, 230(3); 101(6); 57(35); 41(100). M.W. of fulvene = 230.32; M.W. of nitrone = 101.16 The mass spectrum of diphenylfulvene has M^+ = 230 and no 101 peak.	No olefinic protons; Integration: 10 aromatic protons and 18-t-butyl protons.

3. Reaction of 6-Methyl-6-Phenylfulvene and N-t-Butylnitrone

A 0.58 g (3.4 mmol) quantity of methylphenylfulvene was dissolved in a CCl_4 solution of excess N-t-butylnitrone. The mixture was heated under nitrogen at 70° for 4.5 hrs. Three fractions were isolated by plc (25%, 1 elution, uv detection). The nmr spectrum of the fastest moving fraction of 40 mg was recorded and the sample discarded.

Fraction 2 was shown to be a mixture of two products by tlc. A methyl proton absorption at δ 2.12 ppm in the nmr spectrum indicated that no addition occurred across the exo double bond. The integrated ratio of the aromatic proton absorptions at δ 7.20 and the t-butyl proton absorptions at δ 1.07 and δ 0.96 is 5:9, respectively. The components of the mixture were then two of the four possible thermally

allowed one-to-one cycloadducts. The parent peak of the mass spectrum of Fraction 2 was 269, and the products were isolated in 67% yield. See Nmr Spectrum No. 78.

Fraction 3 was shown to be a mixture of two or more components by tlc. The nmr spectrum of the mixture had a methyl proton absorption at δ 2.12 and no olefinic proton absorptions in the region δ 5.0-7.0. The integrated ratio of the aromatic proton absorption and the t-butyl proton absorptions in the nmr spectrum was 5:18, respectively. It follows that Fraction 3 was a mixture of two or more of the eight possible two (N-t-butylnitrone) to one (6-methyl-6-phenylfulvene) cycloadducts. The products were isolated in 28% yield.

4. Reaction of 6,6-Diphenylfulvene and C-Phenyl-N-Methylnitrone

C-phenyl-N-methylnitrone (0.22 g, 1.6 mmol) and diphenylfulvene (0.38 g, 1.6 mmol) were dissolved in ~ 5 ml of xylene and the solution was heated under nitrogen at 140° for 17 hrs. The mixture was placed on a plc plate and eluted once with 10% ethyl acetate in cyclohexane and once with 6% ethyl acetate in cyclohexane. Four products were isolated - two as sharp melting solids. Data for the four possible one-to-one cycloadducts are summarized below. The tetrasubstituted exo double bond of the fulvene is, of course, unreactive.[67]

Product	Yield (% Theo.)	mp	Uv Spectrum (Cyclohexane)
A	28	127-128°	287 (ε 19,000)
B	9		
C	19		
D	21	183-184°	207 (ε 45,000)

The parent peak in the mass spectrum of each product was 365. The nmr spectrum of each compound had olefinic proton absorptions in the region δ 5.0-7.0.

5. Reaction of 6,6-Dimethylfulvene and C-Phenyl-N-Methylnitrone

C-phenyl-N-methylnitrone (1.0 g, 7.5 mmol) and dimethylfulvene (3.3 g, 31.4 mmol) were dissolved in ~ 10 ml of benzene and heated under nitrogen at 80° for 4 days. A portion of the reaction mixture was placed on a plc plate and eluted once with 5% ethyl acetate in cyclohexane and once with 2% ethyl acetate in cyclohexane. Products were extracted from the silica gel with methylene chloride. Data for the reaction is summarized below.

Product	Yield	mp	Mol.Wt.
A	45%	120.5-123°	347
B	23%	175-176°	241
C	8%		347
D	24%		241

Molecular weights were determined from mass spectra. The lower molecular weight products are one-to-one adducts while the higher molecular weight products are two (fulvene) to one (nitrone) adducts. Nmr spectra were recorded, but no structure assignments were made.

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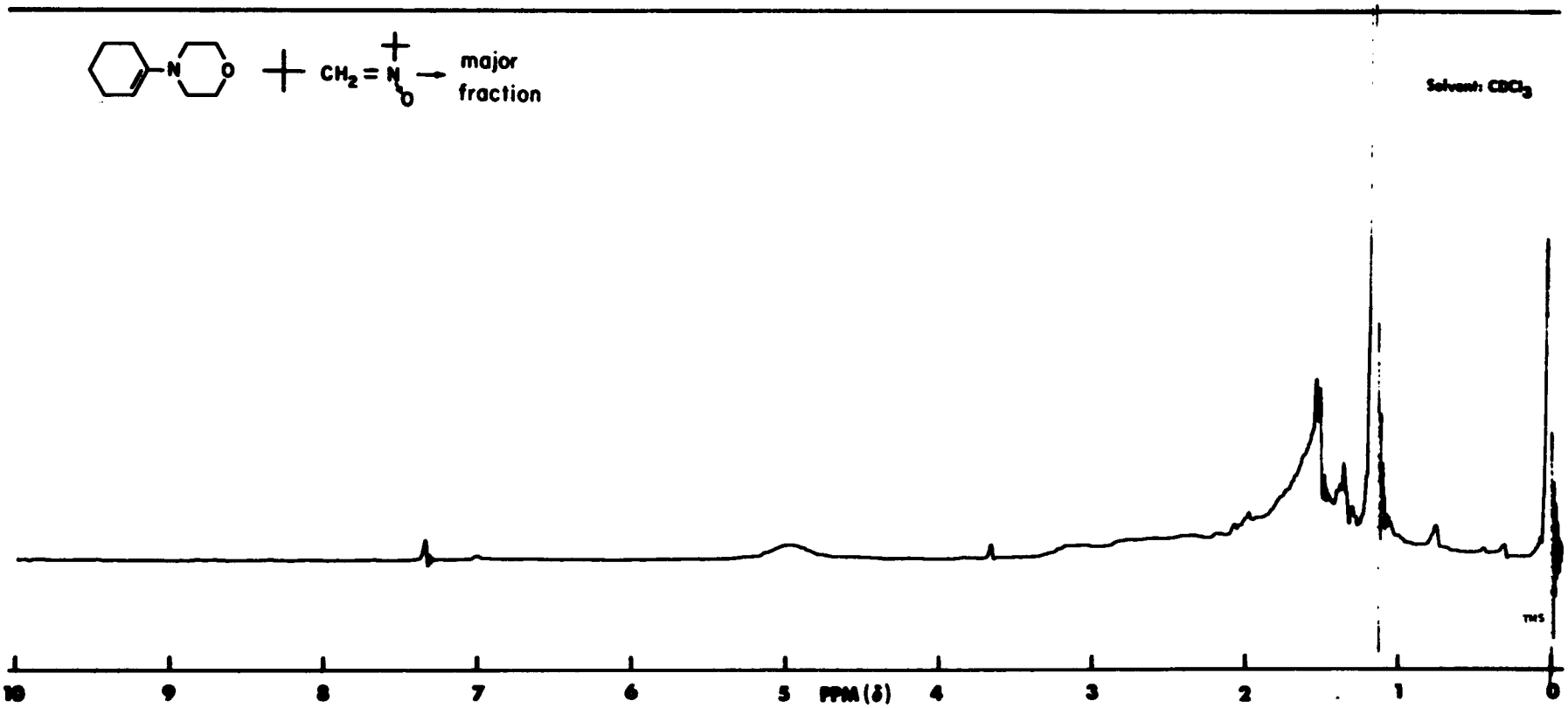
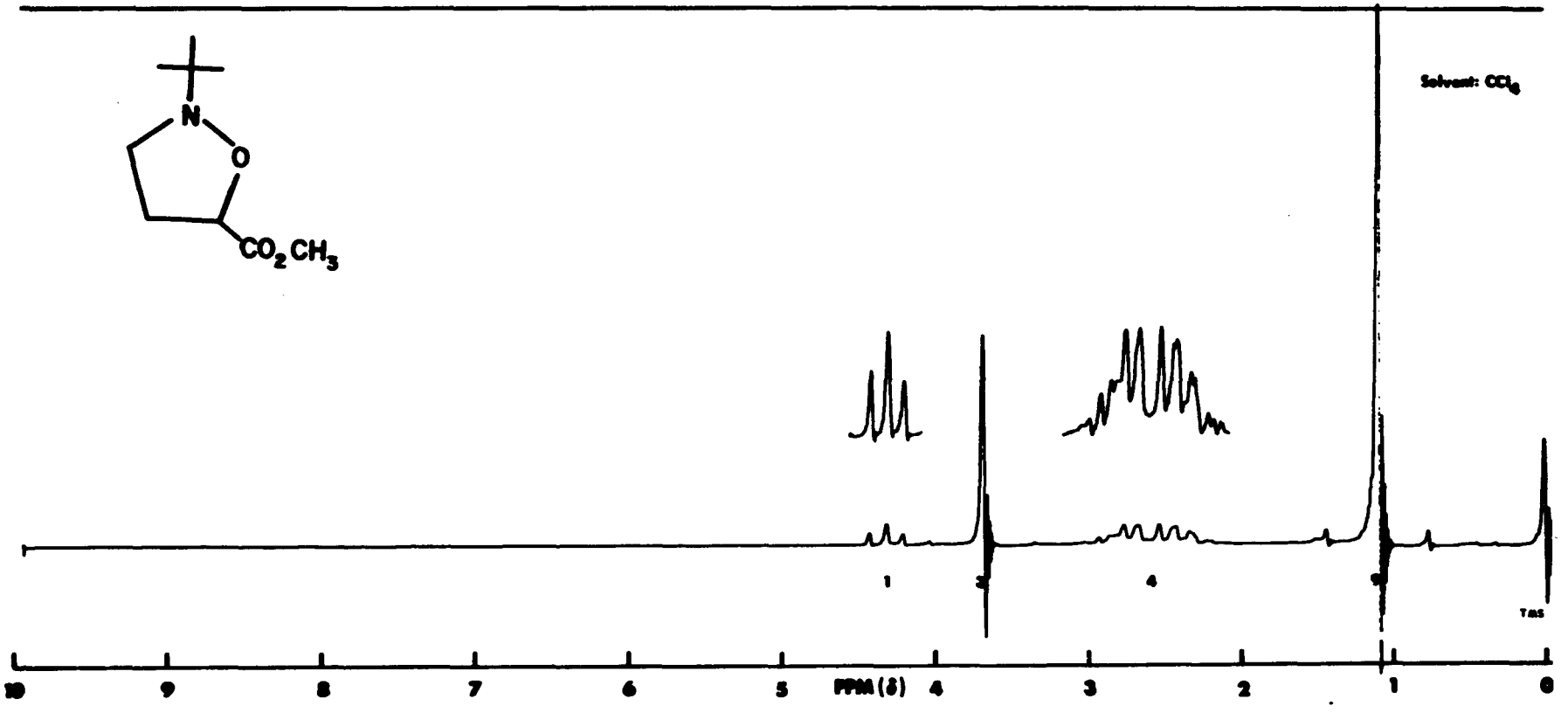
APPENDIX A



Nmr Spectrum of Compound Number 40



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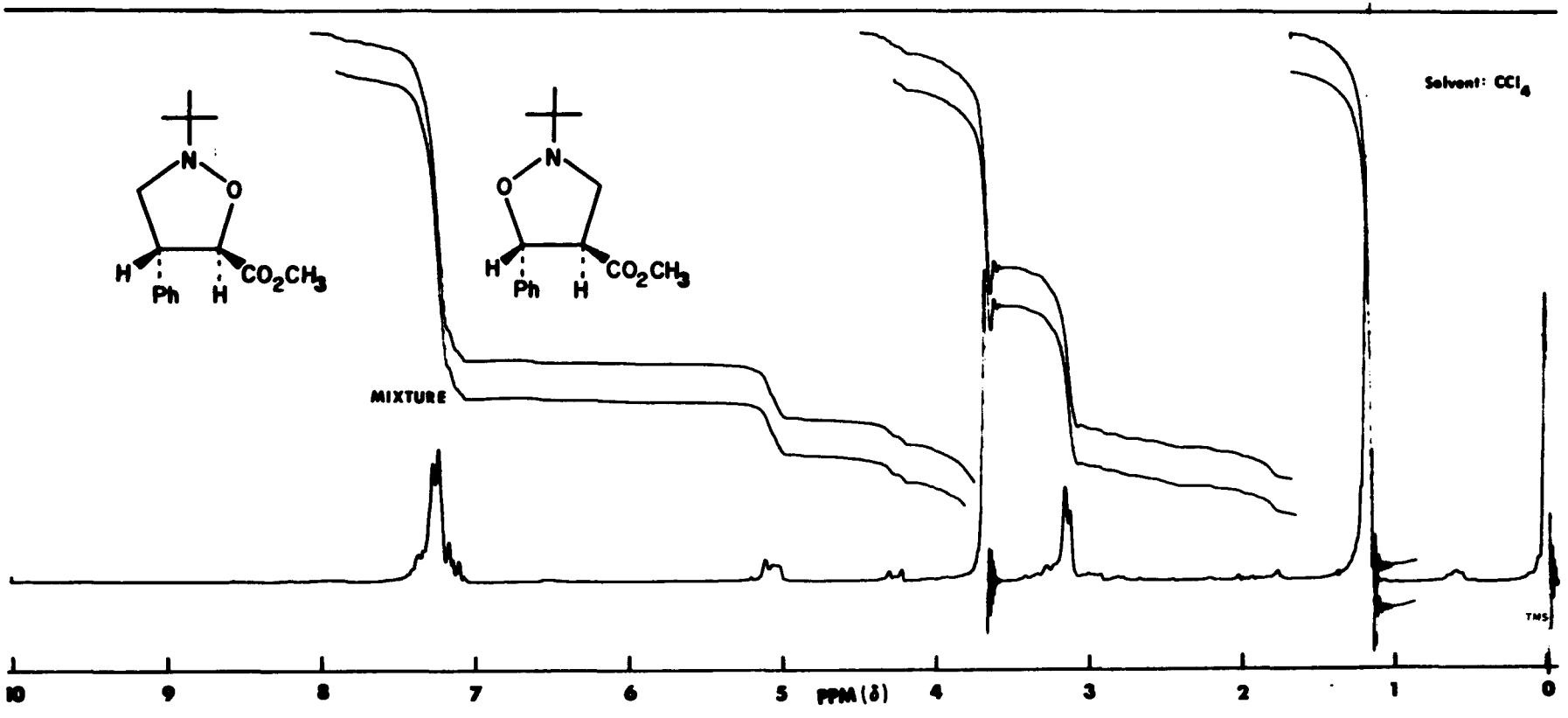
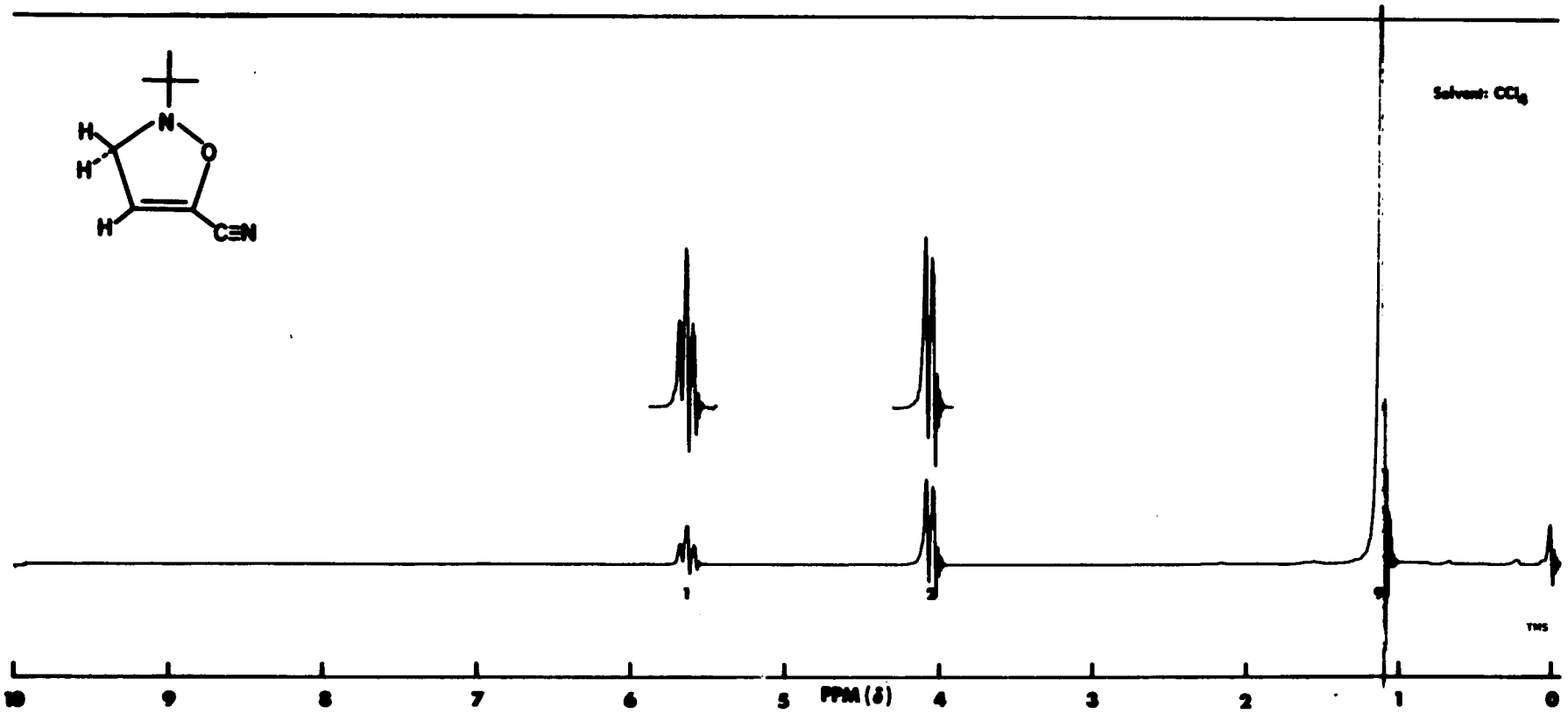


Nmr Spectrum of Compounds Numbers 45 and 46



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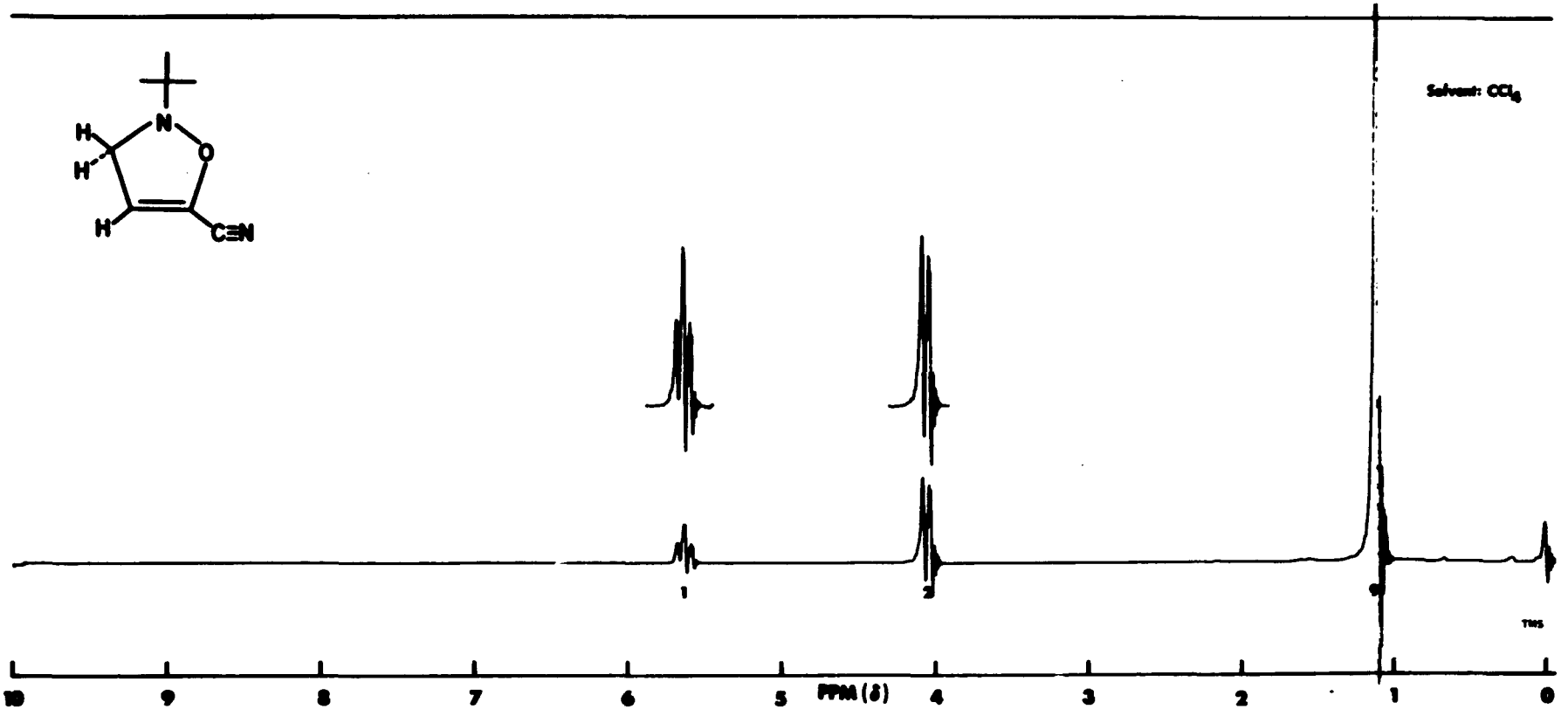
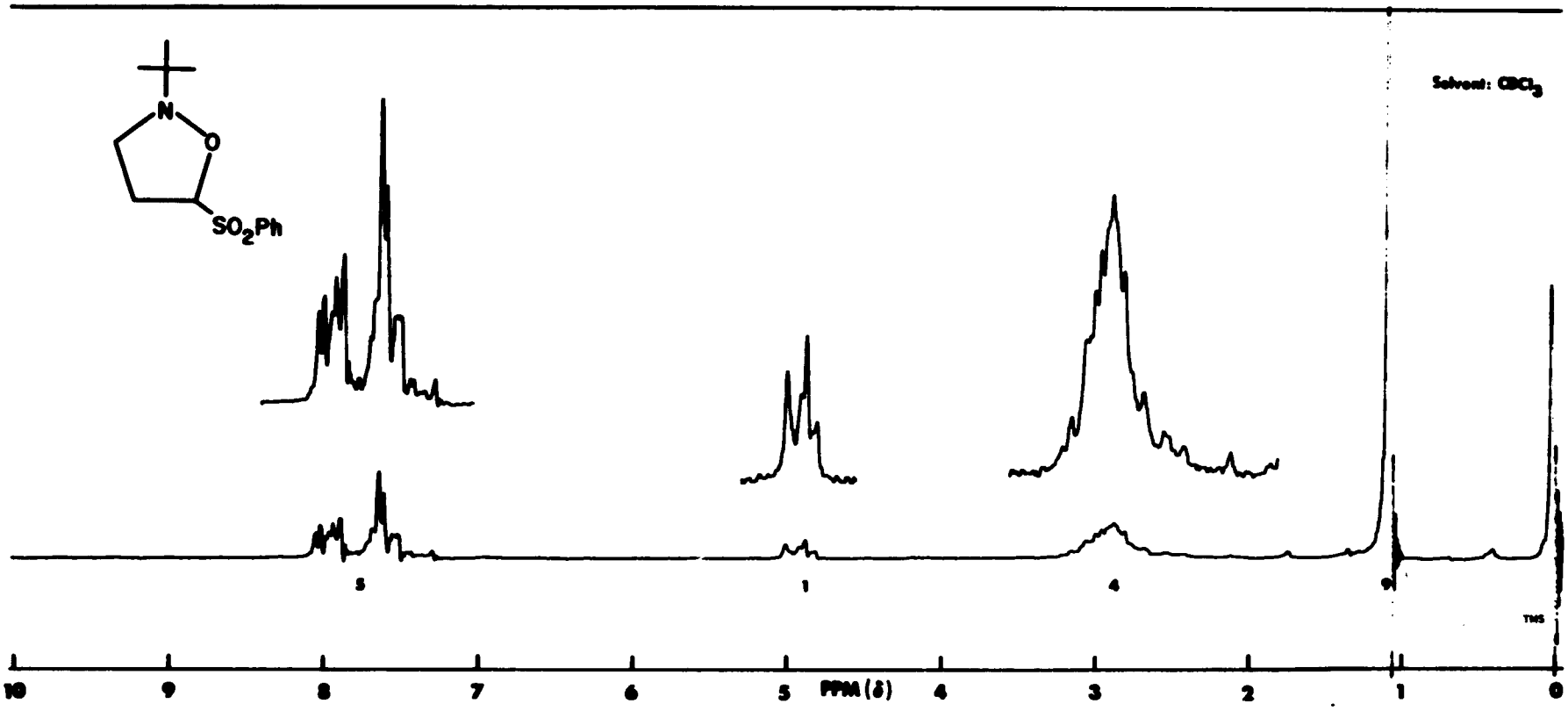


Nmr Spectrum of Compound 52a



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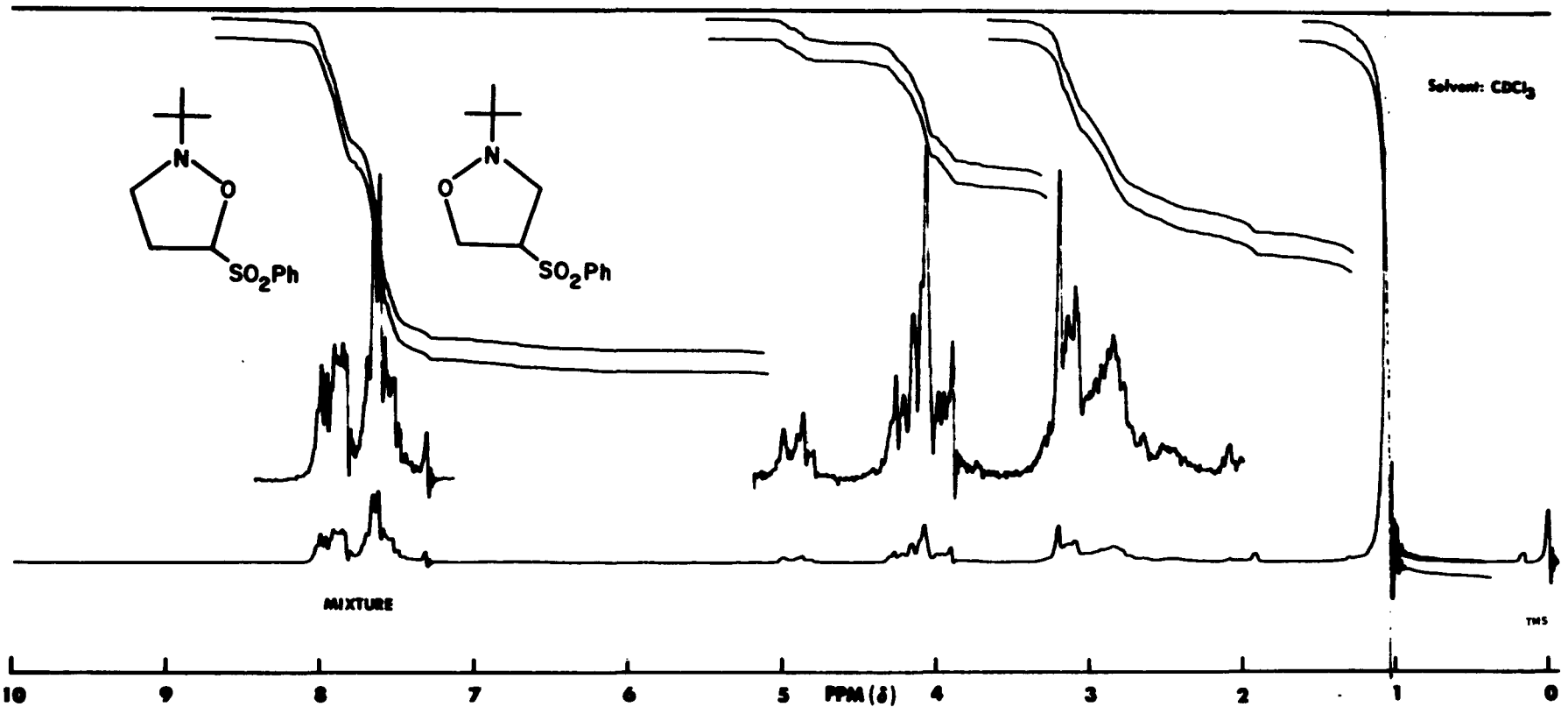

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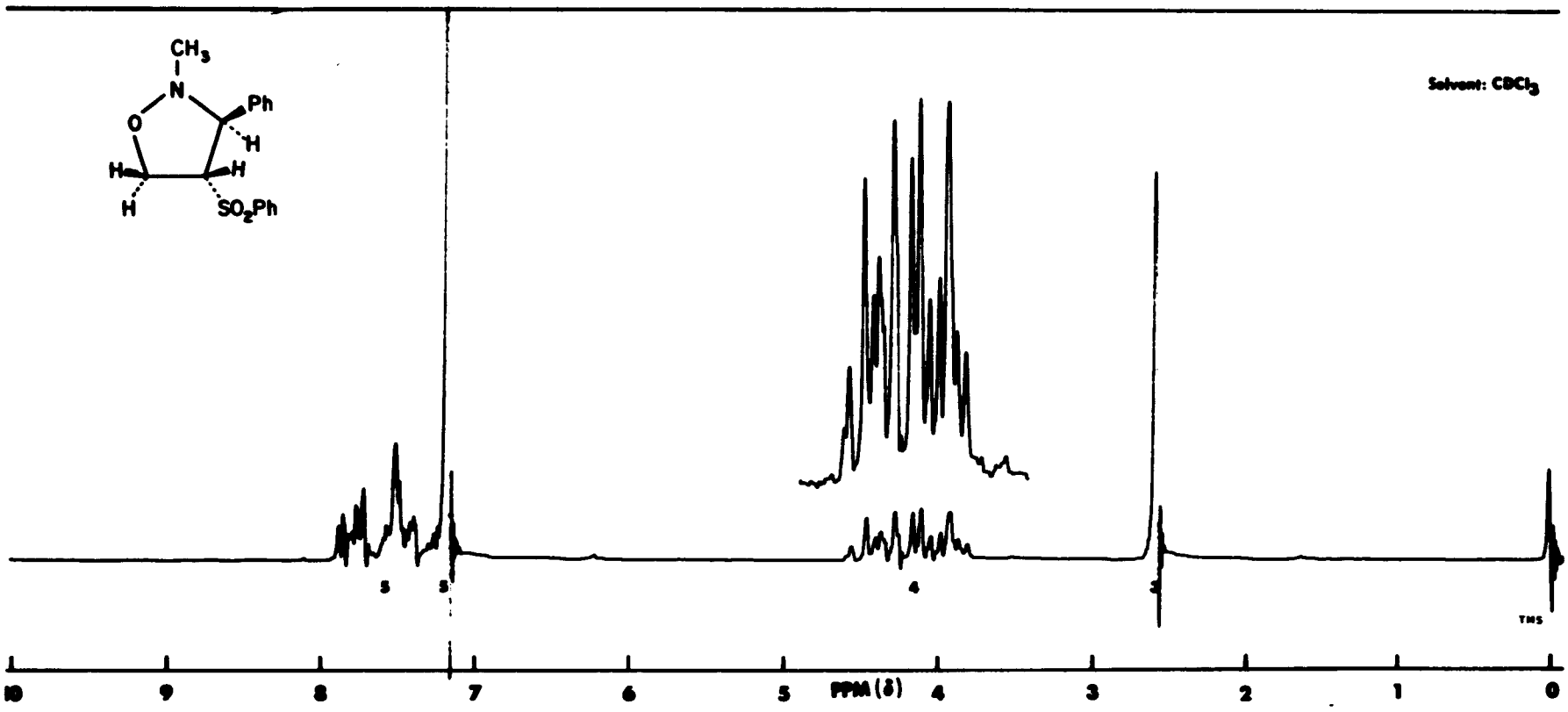

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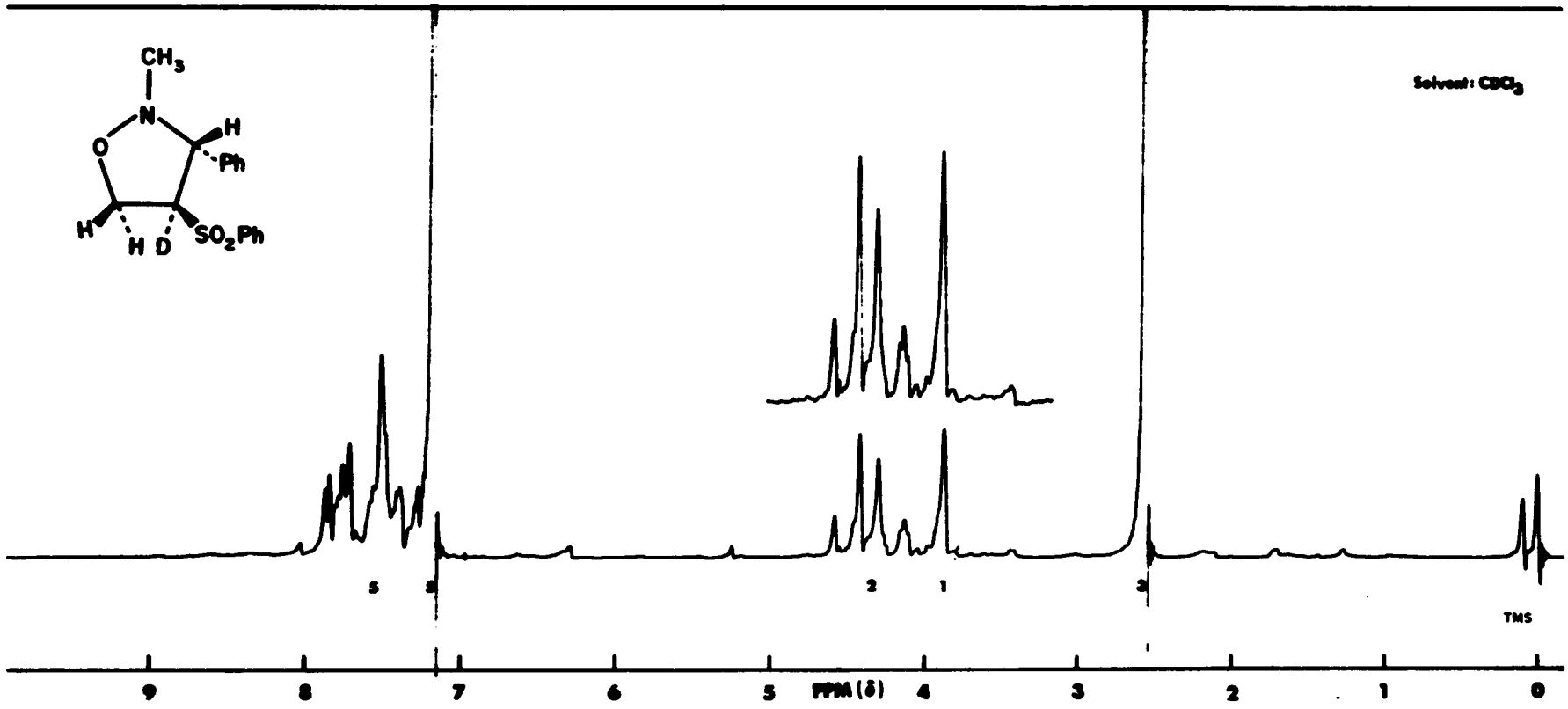

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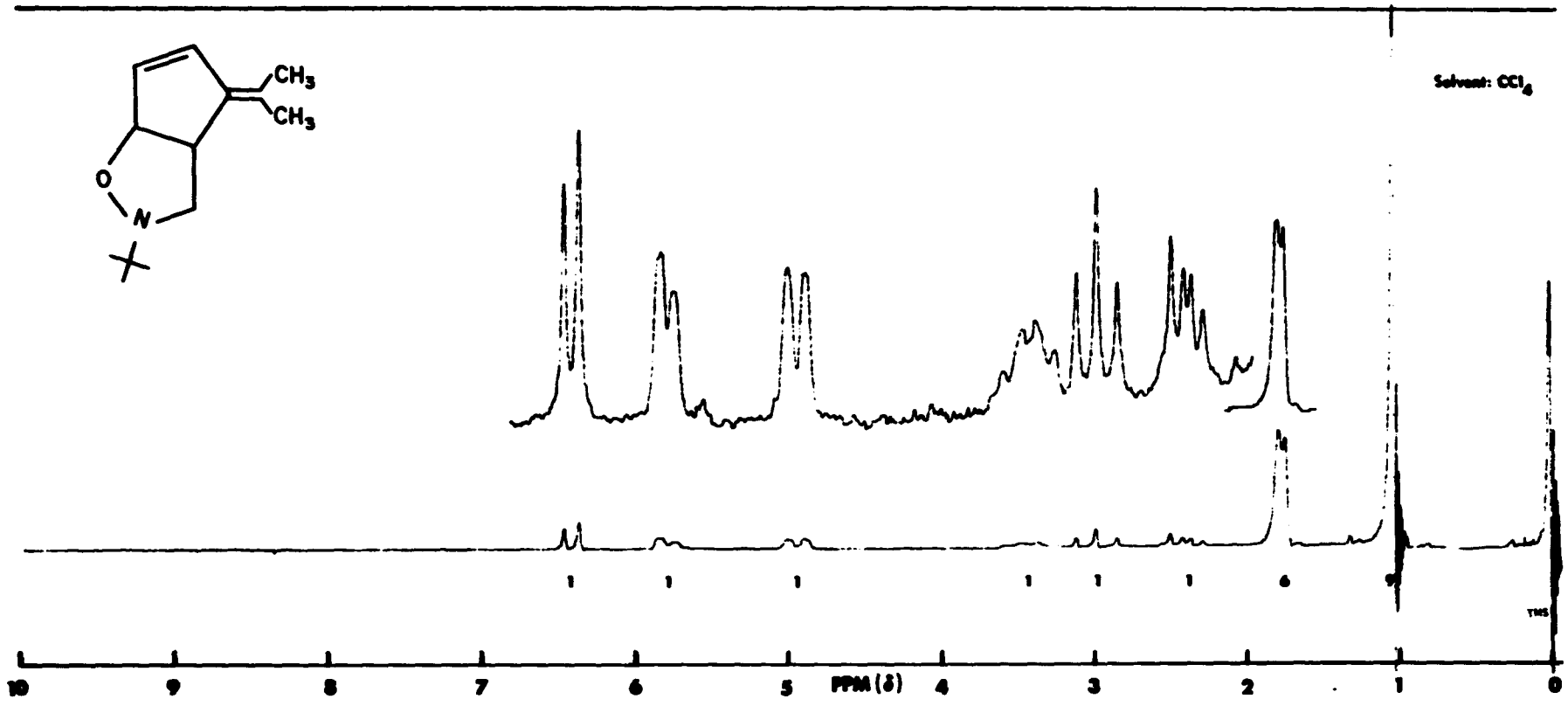

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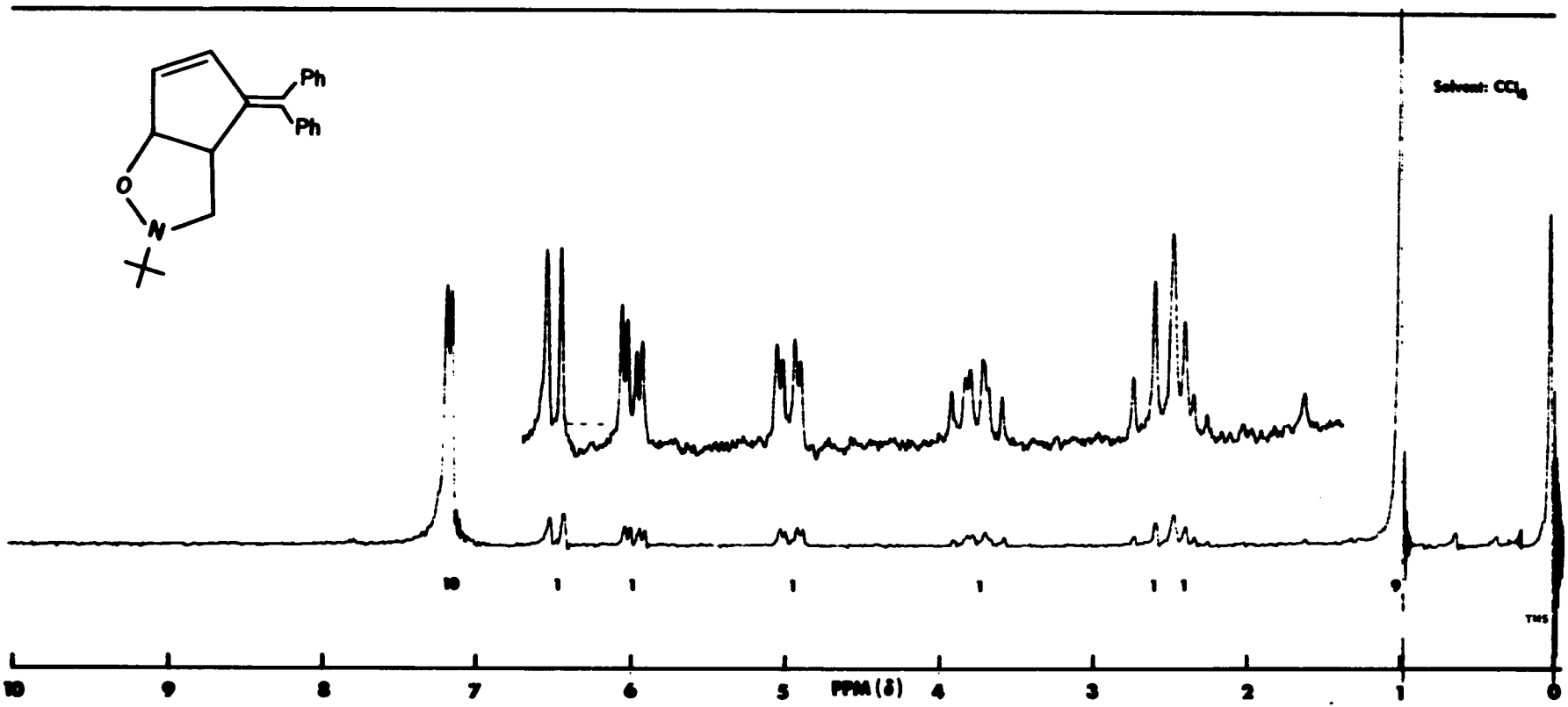

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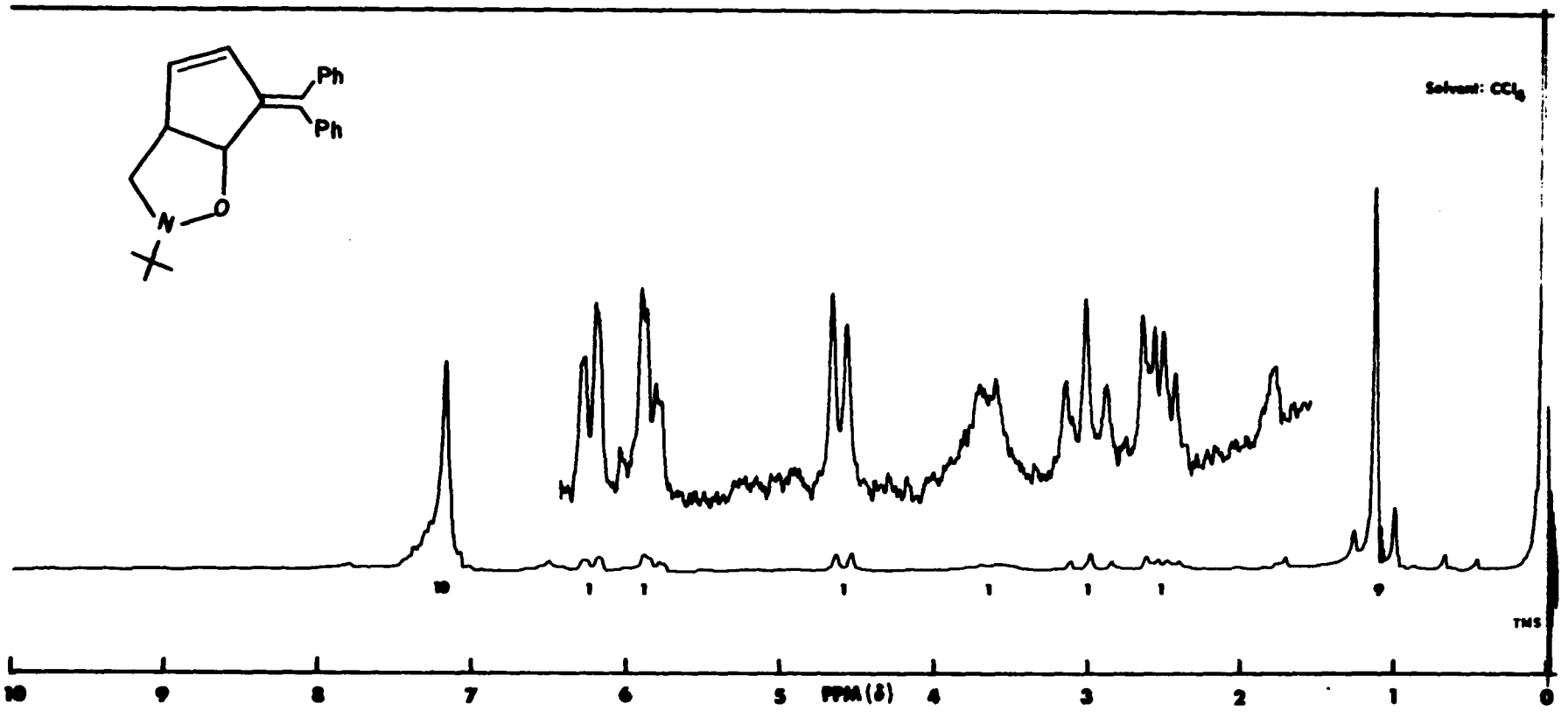

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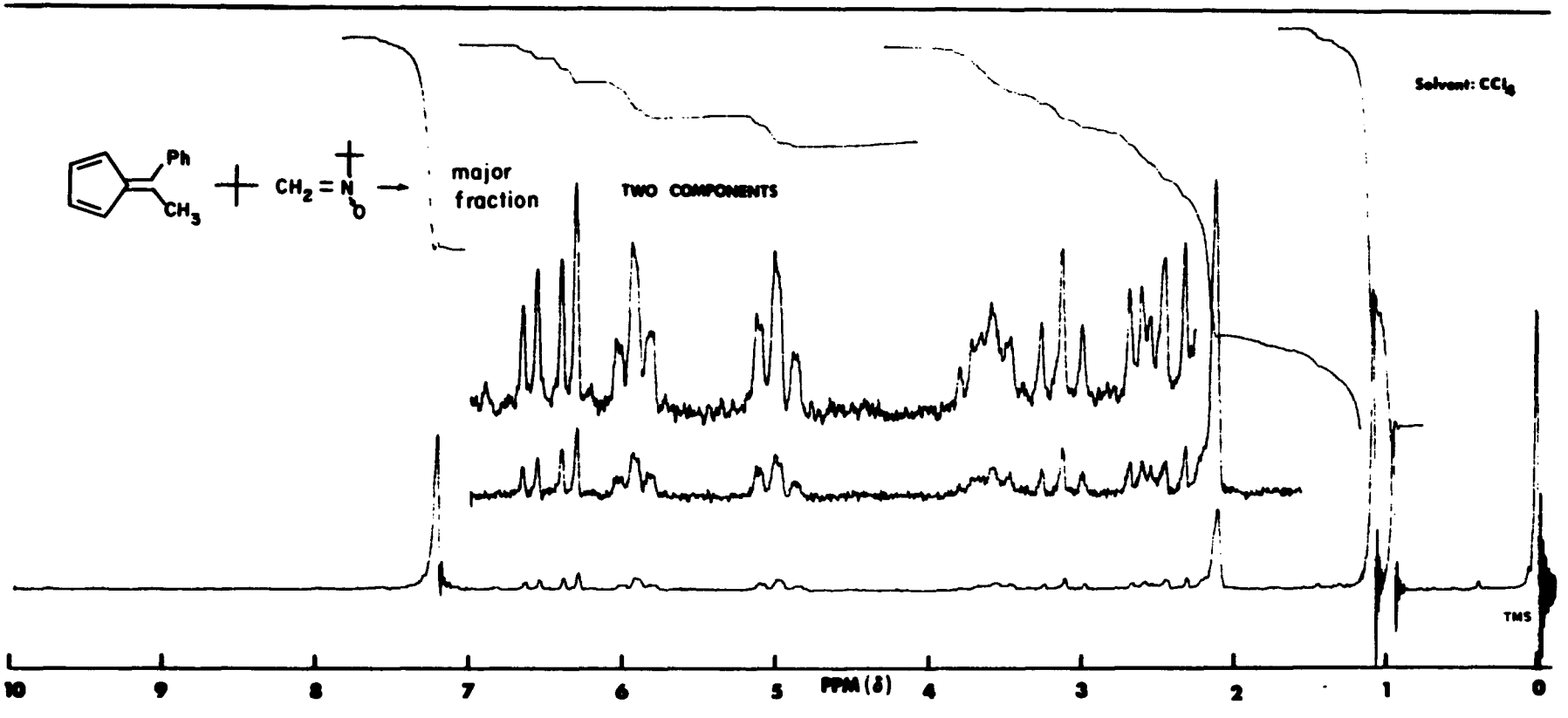
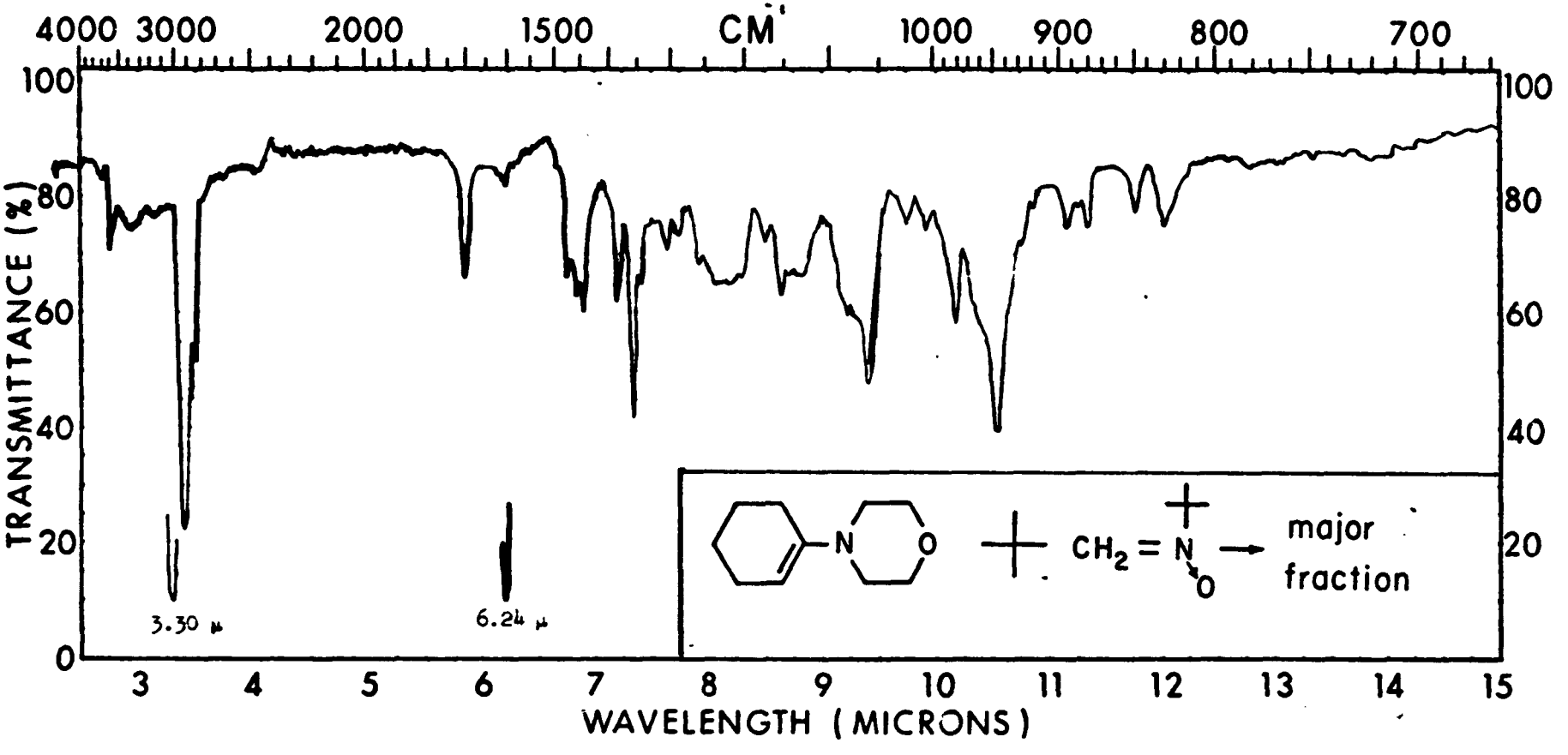


Nmr Spectrum of Compound Number 78

APPENDIX B



Ir Spectrum of Compound Number 40

VITA

Joyner Sims was born June 24, 1943, in Marianna, Florida. He was educated in the public schools of Jackson County Florida, and graduated from Marianna High School in 1961. He was granted an A.A. degree from Chipola Junior College in 1963, a B.S. degree from Florida State University in 1965, and a M.S. degree from Florida State University in 1966. He was employed as a physics and physical science instructor at Gulf Coast Junior College, Panama City, Florida, during the 1966-67 school year. Since 1967, he has been employed as an instructor of chemistry at Chipola Junior College, Marianna, Florida. Presently, he is on Extended Professional Leave to complete the requirements for a degree of Doctor of Philosophy.

He is married to the former Nina Greer Evans, and they are the parents of a daughter, Myla Greer Sims, who is five years old.

EXAMINATION AND THESIS REPORT

Candidate: Joyner Sims

Major Field: Chemistry

Title of Thesis: Cycloaddition Reactions of Nitrones

Approved:

K. N. Houk
Major Professor and Chairman

James B. Traynham
Dean of the Graduate School

EXAMINING COMMITTEE:

Robert V. Hoffman

Eugene W. Berg

Philip W. West

James B. Traynham

Date of Examination:

July 23, 1973